JAN 13 1928

VOL. CLXXV, No. 1 JANUARY, 1928 No. 670

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

ANATOMY OF THE BRAIN FROM A CLINICAL POINT OF VIEW. By FRIEDRICH VON MÜLLER, M.D. 1

TUMORS OF THE BRAIN AND SYPHILIS. By FREDERICK P. MOERSCH, M.D. 12

A BRIEF DISCUSSION OF THALAMIC SYNDROME WITH A CASE REPORT. By E. S. GURDJIAN, M.D., PH.D. 18

AN UNUSUAL CASE OF DIABETES MELLITUS: DEATH AFTER THIRTEEN YEARS' OBSERVATION; NECROPSY. By A. H. GORDON, C. L. CONNOR and I. M. RABINOWITCH . 22

CAROTINEMIA. By WILLARD C. STONER, M.D. 31

THE USE OF DEXTROSE IN THE TREATMENT OF OBESITY: WITH SPECIAL REFERENCE TO THE REDUCTION OF THE BODY WEIGHT WITHOUT MARKEDLY LOWERING THE DAILY CALORIC INTAKE. By BURGESS GORDON, M.D., and E. VON STANLEY, B.S. . 37

UNUSUAL TYPES OF HEMORRHAGIC DISEASE. By HERBERT Z. GIFFIN, M.D. . . . 44

THE IMMEDIATE EFFECT OF ARTERIAL LIGATION: AN EXPERIMENTAL STUDY. By HERMAN E. PEARSE, JR., A.B., M.D. 49

FIVE YEARS' EXPERIENCE IN THE TREATMENT OF CHRONIC AURICULAR FIBRILLATION WITH QUINIDIN SULPHATE. By E. P. MAYNARD, JR., M.D. 55

BALL THROMBUS IN LEFT AURICLE: A CASE REPORT. By GEORGE W. COVEY, M.D., R. CROOK, M.D., and FLOYD L. ROGERS, M.D. 60

BRUCELLA MELITENSIS (ABORTUS) BACTEREMIA ASSOCIATED WITH ENDOCARDITIS. By R. W. SCOTT, M.D., and O. SAPHIR, M.D. 66

ACTINOMYCOSIS: A REPORT OF FIVE CASES—WITH FOUR AUTOPSIES—TWO SHOWING INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM. By P. O. SNOKE, M.D. . 69

CARCINOMA OF ESOPHAGUS: A REPORT OF FIFTY CASES. By JULIUS SHERMAN, M.D. 79

THE DIAGNOSTIC VALUE OF DUODENAL DRAINAGE IN GALL-STONE DISEASE: WITH SPECIAL REFERENCE TO THE SIGNIFICANCE OF SO-CALLED BILIRUBIN CALCIUM PIGMENT. By G. M. PIERSOL, M.D., H. L. BOCKUS, M.D., and HARRY SHAY, M.D. . 84

USE OF FASTING DONORS IN BLOOD TRANSFUSIONS: A PRELIMINARY REPORT. By WALTER V. BREM, M.D., A. H. ZEILER, M.D., and ROY W. HAMMACK, M.D. . . 96

BILE PIGMENTS AND BILE ACIDS OF THE BLOOD IN JAUNDICE. By HOWARD F. SHATTUCK, M.D., ICHIRO KATAYAMA, M.D., and JOHN A. KILLIAN, PH.D. . . 103

INDEX TO PHYSICIANS' SUPPLIES . . . . . ADV. PAGE 46

Contents continued on page x

OWNERS AND PUBLISHERS
LEA & FEBIGER
PHILADELPHIA

COPYRIGHT, 1928, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

Tablets
THYROID
Desiccated
Lederle

Each grain of THYROID TABLETS (Lederle) is the equivalent of approximately 5 grains of fresh hog thyroid glands.

The powder is assayed to contain 0.23 per cent of organic iodine, in accordance with the requirements of the U. S. P. X.

THYROID TABLETS (Lederle) are indicated particularly in the treatment of conditions resulting from hypothyroidism: such as cretinism, myxedema, defective growth, and obesity.

Supplied in bottles of 100 tablets in the following sizes: 2 grains, 1 grain, ½ grain and 1/10 grain.

LEDERLE
NEW YORK

K

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JANUARY, 1928

ORIGINAL ARTICLES.

ANATOMY OF THE BRAIN FROM A CLINICAL POINT OF VIEW.*

By Friedrich von Müller, M.D.,

PROFESSOR OF MEDICINE, UNIVERSITY OF MUNICH.

I invite you to review with me the anatomy of the brain with reference to its function and pathology. To this purpose, we may make use of some pictures which I have recently drawn and published.[1] My coeditor Dr. Spatz and I have tried to copy Nature as exactly as possible and to avoid all explanations, because the theoretical schedules will change with the course of time and the progress of knowledge; but a good picture of Nature remains true for many years.

The lateral aspect of the brain shows the frontal, parietal, temporal and occipital lobes, the fossa Sylvii and the Fissura Rolandi. This fissura divides the motor area with its gigantic motor ganglion cells from the sensory convolutions of the parietal lobe, whose architecture is of entirely different microscopic appearance, and we may say that the extension of the field of visual conception in the occipital lobe is characterized by the white line of Gennari.

A horizontal section of the brain shows the corpus callosum, which acts as a bridge between both hemispheres and thus allows the coöperation of both sides. Destruction of this bridge severely damages the coöperative function: since the intuition and planning of every complicated action is prepared mainly in the left side of the cerebrum, the left hand indeed no longer knows what the right hand is doing, and apraxia is the result. A destruction of the posterior part of the corpus callosum leads to visual disturbances

* Address given at the Mount Sinai Hospital, October 1 and 2, 1926.

and is of importance in the production of mental blindness (Seelenblindheit) or optical agnosia.

When we make a horizontal section below the corpus callosum, we notice the narrow gap of the third ventricle, the hollow space of the primary anterior vesicle of the brain. The gray matter which surrounds this hollow represents the most ancient part of the brain phylogenetically and ontogenetically, and we suppose that the elementary vital and vegetative functions of life have their seat in this mysterious brain substance, the so-called central gray matter.

On both sides of the third ventricle we see the thalamus opticus and the nucleus caudatus, covered by the tela chorioidea. The tela chorioidea, the old covering membrane of the primitive brain vesicle, is of importance because it produces and secretes the cerebrospinal fluid which fills the ventricles and all the cavities of the subarachnoid spaces of the brain and spinal cord. But the tela chorioidea is also a sensitive organ, very rich in sensory nerves, and it is believed that any pressure on the tela chorioidea may produce headache.

The thalamus opticus has nothing to do with visual functions, but it is the old important center of the whole sensibility. The exteroceptive sensations of the skin, the feelings of warmth and cold and those of touch and pain are registered and combined here. The proprioceptive notion of the movements and positions of the limbs, of the tonus of the muscles and of the relation of the body to gravity are sent to the thalamus partly through the way of the cerebellum and of the brachia conjunctiva. Furthermore, we believe that the sensations of pleasure and aversion, or exhaustion and fitness, find their origin in this complicated apparatus, from which conduction fibers lead to the cortex. The cortex is the region of consciousness and memory, where the remembrance of former impressions is stored.

The experience with cases of encephalitis lethargica, the somnolence or insomnia found in that disease, has lead to the belief that the thalamus opticus is the center where sleep and wakefulness are regulated. The older conception that the alternation of sleep and wakefulness is a function of the cerebral cortex is wrong, because the dogs of Goltz and Rothmann, whose cerebral cortex had been completely removed showed the change from waking to sleeping as does the newborn infant whose cerebral cortex is not yet developed. So we come to the conclusion that the thalamus influences and checks the cortical functions.

From the thalamus opticus conductive paths lead to the nucleus lenticularis. The nucleus lenticularis is closely connected with the nucleus caudatus, which is situated anterior and lateral to the thalamus opticus. The nucleus caudatus is separated from the lateral parts of the lenticular body by the frontal part of the capsula interna, a formation of relatively recent origin (phylogenetically).

The nucleus caudatus and the lenticular body have in former times been included under the common name of the corpus striatum, and this old term has been proved correct through modern investigation. The gray matter of the nucleus caudatus and the lateral part of the nucleus lentiformis (the putamen) are of the same character and present the same cellular structure as the third stratum of the cortex. Since we know that the nucleus caudatus and the putamen form a unit, we now group them both under the common name of striatum.

The putamen and the nucleus caudatus have no connection with the brain cortex and receive no fibers from it. They are to a certain extent a primary center. But the corpus striatum receives afferent fibers from the thalamus and sends efferent fibers to the inner part of the nucleus lentiformis. This inner part with its two or three subdivisions is called the nucleus pallidus, and this pallidum is older in development than the striatum. In the newborn child, the pallidum is already ripe and its fibers stain black with the Weigert method, at a time when the putamen is still perfectly free from nerves with myelin sheaths.

We are allowed to believe that a center in the course of its development is ripe for function only when its development is perfected. The development will be perfected only when the nerve fibers have fully developed their myelin sheaths. By staining with the Weigert method, we are, therefore, able to judge if a center has reached its state of maturation and full function. In the newborn child and the early weeks of extrauterine life the whole cortex is still perfectly free from black myelinized nerves. This is especially true of the motor nerve paths which lead from the anterior central convolution in the brain to the pes pedunculi, the oblongata and to the lateral part of the spinal cord. This pyramidal tract is not yet myelinized and, therefore, cannot function. But the newborn infant and even the fetus in the second half of its intrauterine life present extensive movements of ataxic type. The newborn infant shows distinctly in the expression of its face its feelings of discomfort and pain or satisfaction. It cries and is able to suckle at the breast. We are sure that it has visual impressions because it can coördinate its eyes on one point. It can hear and be frightened by noises. It is of interest to compare the state of myelinization and of development with the functions of the newborn infant.

In the newborn infant, the cortex is not yet developed at all, only a small shadow of myelinized fibers is spreading from the thalamus opticus to the posterior central convolution (sensory fibers). But the optic path from the fully developed corpus geniculatum laterale to the occipital region of the fissura calcarina is completely established and so the acoustic path also from the eighth cerebral nerve through the oblongata to the corpus trapezoides, the oliva superior and the posterior corpora quadrigemina is ripe. The oblongata in general is perfectly well established and

here we have to localize the important centers of respiration, the circulatory system, the sucking movements of tongue and lips, and the motion of the face and eyes. In strange contrast to the black color of the oblongata and the upper part of the pons and pedunclular region stands the fact that the pyramidal tract is still perfectly free from myelin.

At this time of life, in the brain only the thalamus opticus and the nucleus pallidus are ripe and because we do not know of motor functions of the thalamus, the nucleus pallidus will be the center of the origin of the movements. It is only the globus pallidus which shows myelin, for the putamen and nucleus caudatus are not yet developed. But the ansa lenticularis, the path of conduction from the sensory thalamus to the motor nucleus pallidus is fully myelinized. Thus a reflex can be established from the sensory to the motor system. One can say that the newborn child represents the type of the thalamopallidar animal.

Centrifugal efferent fibers to the periphery and spinal cord run from the pallidum to the corpus Luys and from there to the nucleus ruber. In this large subthalamic nucleus, we find big motor cells from which the rubrospinal tract of Monakow runs down through the oblongata and the spinal cord. This rubrospinal path in the tegmentum is the principal motor path in most of the vertebrated animals up to the cat and the dog. In monkeys, and especially in man, it diminishes in size and importance and the pyramidal corticospinal path becomes more important. We conclude that in the higher animals movements come more and more under the guidance of the cortex and into the light of consciousness. When the corticofugal motor path is interrupted by a cerebral hemorrhage of the capsula interna, a total degeneration of the pyramidal tract in the oblongata and the lateral spinal tract will result. In this kind of cerebral hemiplegia, the movements of the hands and arms are reduced to a minimum. The movements of the legs are not so much involved, so that in these cases after some time the patient will be able to walk again and to make some other elementary movements of his body. He is able to laugh and to weep and thus he has conserved the expressional movements of his face.

In former times we only studied the loss of movements in the hemiplegic patients. Now we begin to study which kind of movements are left or restored after total destruction of the pyramidal corticospinal tract, and we see that more of the movements are conserved than we previously had supposed. We must conclude that the principal movements of the body, the ability to walk, to stand and sit are left when the older motor system, the pallidum, the nucleus ruber and Monakow's bundle are intact.

Another motor path from the pallidum to the periphery runs in the substantia nigra in the region of the pedunculi cerebri. This big center with its large pigmented cells is surely of a motor nature,

and degenerations and destructions of the substantia nigra produce a one-sided rigor with, or without, trembling. From the substantia nigra efferent fibers join the pedunculi and go with those to the periphery.

The dogs of Goltz and Rothmann, with cerebral cortex perfectly removed, were able to stand and run and to move their limbs. Of greater importance are the observations of Gamper of Innsbruck and others on human children who were born with a perfect defect of the cortex, and where only the nucleus lentiformis, the thalamus and the subthalamic region or less was developed. These unhappy children were able to move their face, body, arms and legs not much less than normal newborn children.

So we see that besides the principal corticospinal pyramidal tract one or two motor paths of older phylogenetic and ontogenetic nature exist, and that these older motor paths conduct the elementary movements of gait, standing, sitting, position of the trunk and, last but not least, the expressional movements of the face and body, chewing, swallowing and other primary functions.

This old motor path is the so-called extrapyramidal tract and has its origin in the pallidum and the nucleus ruber and the substantia nigra.

During the years 1919 and 1920, our attention was drawn to a terrible infectious disease of the brain which we had not noticed before, encephalitis lethargica. In children, the disease begins especially with choreiform movements, in adults more with drowsiness and constant sleep from which the name sleeping sickness has been drawn. Nystagmus and other eye symptoms led to the assumption that the nuclei of the eye muscles were affected, and in the later progress a period of insomnia and finally a general stiffness with some trembling, and a lack of movements, the so-called akinesia of the whole body, produced a picture similar to that seen in Parkinson's disease.

Every voluntary movement can be performed, but only slowly and against some rigor of the muscles. The abolition of automatism, the akinesia, is not only perceptible in the hands, trunk and feet, but lack of mobility is especially pronounced in the face, which is perfectly stiff and shows no longer expression of joy, fear, happiness or other psychic emotion. We call this state amimia.

The anatomic examination of these cases showed that the cortex of the brain, including the pyramidal motor path, was nearly normal and that inflammation and destruction of the ganglion cells was mainly localized in the basal ganglia of the hypothalamic region, the corpus Luys, the substantia nigra, the oliva and to a certain extent in the nucleus lentiformis. The centers showed a dreadful picture resembling a battle field with the dead bodies of the destroyed ganglion cells, surrounded by a swarm of neuronophages and a proliferation of the cellular elements of the neuroglia.

The symptoms of stiffness, rigor, of slowness of gait, combined with some tremor, have long been well known in Parkinson's disease. Pathologic studies of the brain in Parkinson's disease have shown a similar localization, but the involvement is less in the substantia nigra than in the pallidum and in the subthalamic motor centers. Both diseases, therefore, are now known as affections of the extrapyramidal motor system.

We, therefore, see the paradoxical fact that either stiffness and hypokinesia or hyperkinesia with chorea show their localization in the extrapyramidal system, especially in the pallidum, striatum and in the substantia nigra.

It seems rather curious that pathologic affections of a destructive character may be found in the same centers of the brain, as well in those cases where involuntary exaggerated ataxic movements of a hyperkinetic type have been present during life, as in general stiffness. The symptoms of hyperkinesia and hypokinesia seem to be strictly opposite, though the localization of the pathologic and anatomic process is nearly the same.

In both affections (the hypokinetic and the hyperkinetic), the voluntary movements are not really impaired, though they are to a certain extent hindered by the involunatry choreiform movements, the tremor and the stiffness. Stiffness and choreiform movements make the voluntary movements slow and uncertain. The reflexes are normal or only slightly exaggerated; the psychic functions do not suffer severely except in those cases where the disease spreads to the cortex also. Some slowness and hindrance of the psychic functions is not seldom seen as well in Parkinsonism as in Parkinson's disease.

The difference between the hyperkinetic and hypokinetic symptoms, the chorea and stiffness, is not so fundamental as we might think on first impression. We see that encephalitis lethargica often begins with choreiform hyperkinesia and after a while it changes into general stiffness. Parkinsonism and real Parkinson's disease can be combined with or without tremor. Furthermore, the age of the patient is of some influence, and Sachs of New York was the first who insisted on this important point. He pointed out that infantile cerebral hemiplegia (die cerebrale Kinderlähmung) and Little's disease very often are combined with hemichorea and athetosis, while the common hemiplegia in older age almost never shows involuntary movements of the paralyzed limbs.

Sydenham's chorea minor is almost without exception a disease of children, of puberty and sometimes during the first pregnancy of very young women. Sydenham's chorea stands in close connection with rheumatism and endocarditis. But it is sometimes seen also in typhoid fever and other infectious diseases of children; we must suggest that some toxic substance produced by these infections affects certain places of the cerebrum, expecially the nucleus

lenticularis, that this cerebral involvement takes place only in the younger years of life and ends in perfect recovery.

A choreiform disease of more serious character is Huntington's chorea. The involuntary ataxic movements in this disease are very similar to those of chorea minor, and they are also combined with grimaces of the face and sometimes with explosive utterance of cries and invective words. Huntington's chorea is a progressive incurable disease of inherited character, and it slowly leads to mental degeneration. It has been shown that in Huntington's chorea a severe degeneration and atrophy of the whole striatum takes place.

Westphal was the first to describe cases of some stiffness combined with ataxic movements, similar to multiple sclerosis, and he proposed the name of pseudosclerosis. It is a slowly progressing disease which very often begins in childhood. Wilson's disease begins in later years and also shows stiffness, difficulties of movements and sometimes tremor. Strümpell's genius was able to group all those various types under a common point of view, and he has established the conception of the amyostatic syndrome.

Cecile and A. Vogt, in a splendid study, have collected a series of similar cases of hereditary character, and their anatomic preparations have shown that severe atrophy and peculiar histologic changes in the striatum can be found: the "status marmoratus," and now we are sure that pathologic processes of the striatum and pallidum lead to the amyostatic syndrome, to general stiffness, to chorea and athetosis. All these symptoms belong, therefore, to disturbances of the extrapyramidal tract.

The next task was to find out the difference in the anatomic findings between the hypokinetic and the hyperkinetic form, that is, the stiffness on one hand and the choreiform and athetoid movements on the other. And here we find the greatest difficulties. Indeed, we can suggest that a pathologic irritation of motor cells produces involuntary movements and that complete degeneration of the same cells produces paresis, deficiency and loss of motion. But it is also possible that the antagonism between stiffness and chorea can be explained by different localization, such as in the striatum or the pallidum.

C. and A. Vogt followed this line and they have established a clinical syndrome which is due to degenerations of the pallidum or of the putamen and striatum. Jacob Levy and other authors have criticized this distinction, but in the principal point they agree to a great extent with C. and A. Vogt, and from this work we can say that the diseases of the striatum are characterized by ataxic hyperkinesia, athetosis and chorea, while the syndrome of the pallidum shows akinesia and stiffness of the face and body.

If this rule proves true we reach the following conclusions:

A destruction of the pallidum, of the oldest region of the nucleus lenticularis, produces hypokinesis and stiffness. Then it is obvious

that the normal pallidum is the anatomic seat of the normal involuntary movements which accompany our feelings, our psychic motions and all elementary activities which help to complete the voluntary movements.

On the other hand, the degeneration of the caudatum and putamen are characterized by disorderly and exaggerated movements and attitudes. We, therefore, conclude that the putamen and the connected nucleus caudatus are placed superior to the pallidum and that the striatum governs, orders and inhibits the automatic movements of the pallidum. A destruction of the striatum sets the pallidum free, and ataxic, incoördinated and exaggerated involuntary movements then follow.

But there are some difficulties in this explanation however. The findings of the pathologic anatomic investigation are not always in accordance with the rules of C. and A. Vogt. In many cases of general stiffness after encephalitis lethargica, the so-called encephalitic Parkinsonism, the anatomical lesions are not so much found in the nucleus lenticularis, but the substantia nigra shows severe degeneration.

Choreiform movements can be produced not only by affections of the striatum, for Bonhoeffer has shown that severe chorea can be the result of a destruction of the brachia conjunctiva, that is the nervous paths which lead from the cerebellum to the nucleus ruber.

Last but not least, an electric irritation of the striatum does not produce any movements of muscles, while an electric irritation of the motor area of the brain cortex does so.

But if a center gives no motor answer to an electric stimulus, are we then really allowed to say that it possesses no motor function? Is the electric current indeed the adequate stimulus for every nervous center? I do not believe so, and I can imagine that many centers of the brain need another kind of stimulus, perhaps of chemical nature.

With the idea that some part of the nervous centers may react to chemical stimuli, we come to a different conception of the functions and the affections of the brain. I indeed do not believe that the centers of the brain present all the same physiologic type and that they all answer to the same kind of stimulus. They are not like a complicated telephone central station, where electricity is the moving force of all the apparatus.

Pharmacology shows that the drugs and poisons like alcohol, barbituric acid, morphin, caffein, atropin, antipyrin, and so forth, act upon special different functions and centers of the nervous system, some upon the sympathetic or parasympathetic centers, some upon the motor or sensory fibers, some upon the spinal cord and others upon special fields of the brain. These observations show that the drugs and poisons find a special affinity in different parts of the nervous system, or in Paul Ehrlich's terminology, haptophore

groups, and, therefore, we must conclude that different parts of the nervous system show a different chemical constitution. Indeed H. Spatz has shown that there exist some chemical pecularities in certain centers of the brain.

We know that some infectious diseases show the tendency to affect special anatomic parts of the nervous system: acute poliomyelitis is localized especially in the gray anterior column of the spinal cord. The metasyphilitic diseases particularly affect the subarachnoid space, the posterior roots, the posterior tracts and the cortex of the brain. The rheumatic virus, typhoid fever and some other infectious diseases produce in young people an affection of the putamen. Encephalitis lethargica has its localization especially in the subthalamic centers, substantia nigra and oliva inferior.

Such examples of predilection cannot be explained in a mechanical way, they show indeed that some pathogenic microörganisms and their toxins find the best condition for growth and action in different special parts of the nervous system. This predilection for a special localization cannot be explained otherwise than by the assumption that different parts of brain and spinal cord show a different and special chemical constitution.

The sensations of hunger with their automatic contractions of the stomach have been studied by Carlson, and he has found that they are dependent on the deficiency of dextrose in the blood serum. As soon as the concentration of sugar in the blood serum becomes increased by an intravenous injection of glucose, the hunger contractions of the stomach stop. I think the symptoms of hunger may also be produced when the amount of protein in the blood serum sinks so low as we have found in our patients with severe inanition. My brother, Ludwig Robert Müller, was able to show that similar phenomena take place in the case of thirst.

The feelings of hunger and thirst come to our consciousness, and there must be a nervous center which brings this feeling to our knowledge and regulates the appetite. How delightful is the smell of meat to the hungry man and how disgusting after a full meal!

Still finer regulations are required for the maintenance of the isotonic balance in the blood and of the constant hydrogen concentration of the blood serum and the tissue fluids, since we know that under most different conditions the osmotic pressure, the salt content and the neutrality vary only within extremely narrow limits.

There must be a regulatory center, and this center acts under the influence of minute differences of the chemical and physiochemical constitution of the blood. This center must have its place in the central nervous system. We assume that it has its position in the region of the infundibulum and also in the medulla oblongata. The desire for salt and calcium must be regulated somewhere, as soon as their amounts sink below or rise above the normal limit.

All the functions of metabolism show an inclination to produce and maintain an optimum middle ratio.

Diuresis is one of the factors which maintain and regulate the water content of the blood and the body. We know indeed that the regulation of the kidney function is governed by a special chemical substance produced in the hypophysis. It is probable that this secretion is brought into the infundibulum and acts upon the centers of the tuber.

In the gray matter around the third ventricle, we see the nucleus periventricularis, the nucleus tuberis, and the nucleus paraventricularis and supraopticus.

The close relation between the function of smell and the functions of the bladder and the genital functions has led to the assumption that these functions are in close neighborhood to the corpus mammillare.

These vital centers of old phylogenetic origin react not only to chemical stimuli, but also to physical ones. They regulate the body temperature of the isothermic animals. Aronson and Sachs were the first to show that lesions of the basal ganglion centers produce hyperthermia and fever; Hans Horst Meyer has demonstrated that application of cold in certain parts of the corpus striatum produces an increase of oxidation and heat production, and that application of heat lowers the oxidation. The antipyretic drugs probably act upon the same central place.

I do not believe that we ever will be able to outline sharply localized centers of hunger, thirst, or centers for the regulation of salt and water, of equilibrium of body temperature or blood pressure, of sexual instincts and other primary vital functions in the brain. But many hints are given which lead to the assumption that important vital centers are localized in the gray matter around the third ventricle.

Up to this point we have considered the nervous system as a machine and it is a machine indeed, a complicated integration of reflexes from the lowest spinal and sympathetic reflexes up to the reflexes between cerebellum, thalamus and pallidum and finally to the highest functions of the cortex.

In the cortex visual, acoustic and all other sorts of sensory impressions lead to complicated actions under the full light of consciousness. Former impressions and older experiences are stored by memory; they spring up by association and mix their influence with the new event. Some inhibitions may come into play and check the resolution. At last a balance is established and finally an action takes place. This action may take place in the form of speech, writing or movements of all kinds. We must acknowledge that a power of free choice is given to us, and we denominate this power with the term, will. But I do not like to introduce the term of will into the discussion, because it leads at once into the most

difficult questions of philosophy: is the power of free will given to us, or are all our actions determined by other influences? This question has been discussed by the greatest thinkers of the world, by Saint Augustine, Calvin, Kant, Schopenhauer and others. We will do better in medicine to restrict our discussion to the term of consciousness.

When we regard the central nervous system as a machine, where have we to find the origin of the energy which sets this machinery into motion? Where is the spring in this complicated watch, which drives its wheels?

We easily can perceive that the energy, this spring, is of very different power in different men and in the same man at different times. In many people the spring is weak and acts slowly, there is a lack of impulse, a low temperament. The resolution is checked by perpetual doubts. In other, quicker people we see a stronger emotional resonance and a greater source of energy, which wastes its resources. Under the influence of a strong impulse, intemperate people are quickly led to an action before any mental reflection takes place, the reflection follows after the deed, approving or excusing the action, but seldom disapproving and repenting.

Is this vital energy really localized in the brain cortex? I believe it is not. We know that certain organs of the body, especially the endocrine glands, have a pronounced influence upon the mentality. Hyperfunction of the thyroid gland in exophthalmic goiter produces an increased irritability and restlessness of the mental state. A deficiency of the thyroid gland (hypothyroidism) checks and lowers the spirit.

There is no doubt that the sexual organs, ovaries and testes, influence the mentality. It is interesting to see that during puberty the desires do not incline to sexual intercourse, but we see first a certain shyness and shame and the feelings show the finest flower of ideal love.

During the years of fully developed sexual state, the ideas are influenced to a great part by the functions of the gonads and the ideas quickly change after a discharge. Mental interests change also when in older age the gonads have finished their duties.

Carl von Monakow is right when he says that the elementary old instincts of self-preservation and continuance of the race with their wishes and aversions (klisis and ekklisis) are the primary factors of vitality. From these fundamental instincts the impulses (die Triebe) arise in the dark field of unconsciousness, and the impulses influence our ideas and actions in the most intensive manner. Often we are not aware of the real origin of our ideas and wishes, and our fellows know it better than ourselves. The functions of our body and soul lie more than we formerly believed in the mysterious field of the unconscious.

In acute diseases, one of the first symptoms is loss of appetite,

of the impulse to maintain our body. And in severe diseases the whole impulse for preservation of life may be entirely lost. The diseased state of the whole body has influenced the mentality.

So our organs, our glands, our whole body influences our mind. The psychical processes are not only localized in the brain cortex. Life and soul are a function of the entire organism.

Gentlemen, you may ask what have these ideas to do with internal medicine? You will say that this lecture was more in the field of neurology and physiology. But I wished to show that no sharp limits exist between neurology and internal medicine. Many important questions are common to both and belong to the common mother, *general medicine*.

Reference.

[1] Neurologische Wandtafeln von A. Strümpell und Jakob. Zweite Auflage, herausgegeben von Friedrich Müller und Hugo Spatz, München, Verlag von J. F. Lehmann, 1926.

TUMORS OF THE BRAIN AND SYPHILIS.*

By Frederick P. Moersch, M.D.,
ROCHESTER, MINN.

It may seem a far cry to speak of the relationship between tumors of the brain and syphilis, for certainly the clinician rarely need concern himself with the possibility of syphilis in dealing with a suspected brain tumor, and conversely the syphilologist, on obtaining a report of a positive Wassermann reaction on blood or spinal fluid has seemingly established a definite diagnosis, and he courageously sets about to institute a cure.

Fortunately, for all concerned this is the rule and little need be said regarding the remarkable strides made in the diagnosis and treatment of both syphilis and of brain tumors in the last twenty-five years. Unfortunately, however, we forget at times the chameleon-like characteristics of these two affections and some rude exception must occur to wake us from our lethargy. It was such an experience, and the hope that others might benefit from the experience that prompted my review of the cases of brain tumor in the Mayo Clinic.

If one reviews the literature on syphilis of the nervous system and tumor of the brain one finds a great array of material. However, comparatively little can be found which might be a guide in the differential study of such disorders. Kaplan, states that the serology of cerebral tumors is almost negative, that if the Wassermann reaction on the blood serum in a given case of brain tumor

* Read before the Minnesota Neurological Society, Rochester, Minn., June 11, 1927.

is positive one must be more cautious than in any other neurologic disorder and that only an unquestionable positive reaction on the spinal fluid should make one accept syphilis as the cause of the tumor. Lange takes exception to the latter statement and says that a positive Wassermann reaction on the spinal fluid in a case of brain tumor is of little value as it may result from the increase of albumin which produces a nonspecific reaction. Nonne's observations tend to agree with those of Kaplan for he feels that, if the Wasserman reaction on the spinal fluid is positive in a case of brain tumor, in all probability syphilis is also present.

For purposes of discussion, I shall divide my problem into (1) positive Wassermann reaction on the blood in cases of brain tumor; (2) positive Wassermann reaction on the spinal fluid in cases of brain tumor; (3) unusual and confusing data with regard to the spinal fluid in cases of brain tumor; (4) the value of choked discs in the differential diagnosis of tumors of the brain and syphilis.

Positive Wassermann Reactions on the Blood in Cases of Brain Tumor. In a routine examination of about 1000 patients with brain tumor, a Wassermann test on the blood was made with but few exceptions. According to the records the reaction was positive in 18 cases. This is exclusive of several cases in which the diagnosis of brain tumor was not definitely established. It is also exclusive of the cases of gumma of the brain. Of these 18 cases, 13 were verified by operation or postmortem, the remaining 5 were clinical cases in which the diagnosis was more than reasonably positive (Table I).

TABLE I.—POSITIVE WASSERMANN REACTIONS ON THE BLOOD IN CASES OF BRAIN TUMOR.

Age, yrs.	Sex.	Site.	Lesion.	Reactions.		Fundus.
16	M.	Cerebellar tumor	Glioma	++	...	Choked disc.
15	M.	Unlocalized	Clinical case	++	...	Choked disc.
17	M.	Pituitary	Clinical case	+	...	Atrophy.
35	F.	Unlocalized	Clinical case	++++	++	Choked disc.
22	F.	Cerebellar cyst	Glioma ?	++++	...	Choked disc.
7	F.	Cerebellum	Glioma	++++	−	Choked disc.
1.8	M.	Optic thalmus	Tuberculoma	++++	−	Choked disc.
15	F.	Cerebellum	Tuberculoma	++++	++++	Choked disc.
44	M.	Unlocalized	No data	++	...	Choked disc.
52	M.	Basal	Epithelioma	++++	++++	No record.
48	M.	Corpus callosum	Endothelioma	++++	++++	Atrophy.
47	M.	Frontoparietal	Glioma	+++	++++	Negative.
37	M.	Bilateral frontal	Glioma	++++	...	Choked disc.
23	F.	Superchiasmal	Cyst	+++	+++	Pallor.
23*	M.	Right parietal	....	++++	++++	Choked disc.
57	F.	Left frontal	Endothelioma	++++	−	Negative.
50	F.	Metastases	Carcinoma	++++	++++	Negative.
53	F.	Pituitary	Clinical case	++++	++++	Atrophy.

* Decompression performed.

In most of these 18 cases, more than one positive Wassermann reaction on the blood was obtained. In only 4 of the cases was the possibility of syphilis considered seriously. In 1 case (Case X) there was a history of possible syphilis; in 1 case (Case XIII) slight aortitis and moderate round-cell infiltration in the brain were found at postmortem; in 1 case (Case XII) four strongly positive Wassermann reactions on the blood were obtained, and the blood of the patient's wife also reacted positively. In this case, postmortem examination disclosed a glioma of the left frontoparietal area but there were no signs of syphilis. In 1 case (Case XVIII) the history and clinical data were typical of pituitary tumor, namely, characteristic field defect, pallor of the discs and destruction of the sella. Four strongly positive Wassermann reactions on the blood were obtained and in spite of a therapeutic test a steady progression of the symptoms was observed. In these 4 cases examinations of the spinal fluid were entirely negative. It would seem that the diagnosis while not positively established might in all fairness be considered to represent the infrequent association of tumor of the brain and syphilis, although in the fourth case besides the positive reaction on the blood there was no single sign or symptom of syphilis.

The occurrence of a positive Wassermann reaction on the blood in cases of brain tumor is not new, since cases have been reported by Nonne, Marburg, Lange, Stern, Kaplan and others. For a time, an attempt was made to explain these positive reactions on the supposition that the patient also had syphilis. This is hardly tenable although undoubtedly brain tumor and syphilis do coëxist, as may have been possible in these 4 cases, and in cases reported in the literature.

It would seem, that with more careful clinical and pathologic investigation, that the positive Wassermann reactions occurring in cases of brain tumor are not an index of syphilis. In 2 cases of this series, malignancy was considered as the causative agent in the nonspecific reactions (Cases X and XVII). There were 2 cases of tuberculoma (Cases VII and VIII) which also brings up the question of the nonspecific reactions in this disease.

Positive Wassermann Reaction on the Spinal Fluid in Cases of Brain Tumor. In 11 of the 18 cases, the Wassermann reaction on the spinal fluid was made and a positive reaction was obtained in 1 case. Evidence of syphilis could not be found in this case either clinically or at operation. In 1 case of the series the reaction was positive on the spinal fluid but it was negative on the blood serum. Obviously all such patients are not given this examination, therefore the percentage value is low (Table II).

A consideration of these two groups of cases will show that a positive Wassermann reaction on the blood, while infrequent, cannot be said to be uncommon, and that a positive reaction on the spinal fluid does not definitely indicate syphilis.

As has been stated, there was no reason why it should be assumed that the positive serologic tests were directly due to syphilis except in 4 rather questionable cases. Even in the 2 cases in which the reaction on the spinal fluid was positive, the presence of a neoplasm was demonstrated, and so far as could be determined there was no evidence of syphilis. It would appear that as a result of certain physical or physiologic factors, certain changes take place, and account for these false positive reactions.

TABLE II.—POSITIVE WASSERMANN REACTION ON THE SPINAL FLUID IN CASES OF BRAIN TUMOR.

Age and sex.	Site.	Lesion.	Blood Wassermann.	Spinal fluid.			
				Wassermann.	Nonne.	Small lymphocytes.	Colloidal gold.
57 F.	Left frontal	Endothelioma	++++	++++	+	1	1233322100
			−	+	+	1	222220332333
35 F.	Basal ganglia	Glioma	−	++++	−	1	
			−	−	+	1	

Although there are fewer cases on record of positive reactions on both blood and spinal fluid than on the blood alone, there are enough to warrant the assumption that these observations are not mere accidents. Thus Stern reports a case of a gliosarcoma of the cerebellopontile angle in which the reaction on the blood and spinal fluid was positive. Lotmar, Newmark, and others report such cases. Nonne goes so far as to say that if the reaction is positive syphilis must be present. This is contrary to my observations, which are more in accord with those of Lange.

It should not be assumed from the foregoing that a syphilitic person is immune to brain tumor since they do occur in such cases as evidenced by records and reported cases.

Unusual and Confusing Data with Regard to the Spinal Fluid in Cases of Brain Tumor. This group consists of cases in which the history is suggestive of brain tumor and examination of the spinal fluid reveals unusual features (Table III).

The confusing features in this group of cases might lead the inexperienced observer to a diagnosis of syphilis rather than brain tumor. In my experience the occurrence of pleocytosis must not mediate against brain tumor, particularly if the tumor is situated either on the cortical surface or along the ependymal lining. Smith, in a series of 102 verified cases of brain tumor, found a great variation in the pleocytosis but does not mention a positive Wassermann reaction. It is likely that the occurrence of pleocytosis in cases of brain tumor led the Germans to practice the therapeutic "smear

cures." Even with negative data the question of syphilis is frequently so outstanding that therapeutic tests have been resorted to. Morrison and McKinley, Noehte, and Jooss report cases in which tentative diagnoses were made of syphilis and therapeutic tests were employed but postmortem examinations revealed tumors.

TABLE III.—UNUSUAL SPINAL-FLUID REACTIONS.

Age, yrs.	Sex.	Site.	Fundi.	Blood Wassermann.	Spinal fluid.					Remarks.
					Wassermann.	Nonne.	Small lymphocytes.	Polymorphonuclears.	Colloidal gold.	
38	M.	Pituitary	Atrophy	−	−	−	24	...	.....	Tumor partially removed.
33	M.	Pituitary	Atrophy	−	−	+	33	...	1223332210	Tumor partially removed.
34	M.	Right frontal	Choked disc	−	−	+	45	20	.....	Glioma.
54	M.	Corpus callosum	−	−	−	+	125	556	000123333	Glioma.
48	M.	Cerebellomedullary	Choked disc	−	−	+	55	...	4555554320	Endothelioma.
49	F.	Acoustic	−	−	−	+	2	...	0144535421	Yellow fluid; neurofibroma.

Although I have observed variable colloidal-gold curves in cases of brain tumor, my experience coincides with that of Ayer and Solomon that there is no constant curve in such cases.

Naturally the question of an inflammatory process must be kept in mind in these cases since encephalitis, ependymitis, or arachnoiditis may occur and present a clinical picture of brain tumor. However, the consideration of inflammatory conditions presents an added phase which seems rather separate from that of brain tumor and syphilis.

The Value of the Choked Disc in the Differential Diagnosis of Tumors of the Brain and Syphilis. It is the usual assumption that in the presence of a true choked disc, in all probability brain tumor will also be found. This, of course, to the experienced clinician, is a fallacy, since many factors may influence the production of a choked disc. One may, therefore, emphasize the fact that the mere occurrence of a choked disc associated with positive serologic tests must not be interpreted as indicating a brain tumor in preference to syphilis. It may be noted in Table I that a choked disc was present in most of these cases, but it cannot be taken as conclusive evidence of its diagnostic significance. This leads to a consideration of the opposite problem, that is, making a clinical diagnosis of brain tumor which later proves, on serologic investigation, to be syphilis. This experience is not as common as is the diagnosis of syphilis in a case of brain tumor. The cases presented in Table IV might all be con-

sidered to present the brain tumor syndrome, that is, the clinical history might be accepted as that of brain tumor and on examination the so-called cardinal signs of brain tumor were present, choked disc, headache, vomiting and progression. Serologic tests, however, proved to be definitely positive; under treatment the patients either improved or recovered, and there were no further evidences of tumor.

TABLE IV.—SYPHILIS OF THE NERVOUS SYSTEM AND CHOKED DISCS.

Age, yrs.	Sex.	Fundi.	Blood Wassermann.	Spinal fluid.					Remarks.
				Wassermann.	Nonne.	Small lymphocytes.	Polymorphonuclears.	Colloidal gold.	
44	F.	Choked disc	++++	++++	+	20	...	555553100	Improved; died later.
32	M.	Choked disc	++++	++++	+	35	11	012220233331	Recovered.
45	F.	Choked disc	++++	++++	−	5	...	.....	Recovered.
37	M.	Atrophy	++++ ++++	++++	+	28	...	2345421000	Improved.
52	M.	Choked disc	−	++++	+	37	...	.....	Recovered.
28	F.	Choked disc	+++	−	−	3	...	.....	Recovered.

Comment. As has been stated it was necessary to consider the possibility of brain tumor in all of these cases. Most of the patients were sent to the Mayo Clinic with the preliminary diagnosis of brain tumor. The difficulty of making a differential diagnosis in the presence of positive serology is obvious, especially in cases in which the test on the spinal fluid was also positive. A study of the tabulated data (Tables I to IV) will demonstrate that none of the serologic data, the condition of the fundus nor any one cardinal symptom are pathognomonic of either brain tumor or syphilis.

To this group of possibilities must be added the converse, that the presence of a choked disc cannot be accepted as pathognomonic of brain tumor either in the presence or absence of positive reactions on blood and spinal fluid. A diagnosis in such cases should only be attempted if there is no response to a therapeutic test, assuming that the patient is seen at a time when a therapeutic test is possible. It is well at this time to emphasize Kaplan's assertion that "we must not forget to treat the patient and not the serology."

Conclusions. 1. Tumor of the brain is sometimes incorrectly diagnosed as syphilis because of: (*a*) Positive Wassermann reaction on the blood; (*b*) positive Wassermann reaction on the blood and spinal fluid; (*c*) positive Wassermann reaction on the blood and an unusual condition of the spinal fluid; (*d*) negative Wassermann reaction on the blood but positive reaction on the spinal fluid; (*e*)

negative Wassermann reaction on the blood but an unusual condition of the spinal fluid.

2. The diagnosis of brain tumor is frequently made because of choked disc in spite of serologic changes.

3. The incidence of choked discs in cases of syphilis is frequent enough so that its presence in cases of suspected brain tumor should not be accepted as a positive differential point.

BIBLIOGRAPHY.

1. Ayer, J. B., and Solomon, H. C.: Examination of the Cerebrospinal Fluid from Different Loci, The Human Cerebrospinal Fluid (Association for Research in Nervous and Mental Disease), New York, Paul B. Hoeber, 1926, Chap. V, p. 84.

2. Dufour, H., and Semelaigne, G.: Considérations sur la nature des elements cellulaires du liquide céphalorachidien dans un cas de sarcome fusocellulaire du cerveau, Rev. neurol., 1920, **36**, 74.

3. Jooss, C. E.: Ueber einen mit Salvarsan behandelten Fall von malignem Gehirntumor, München. med. Wchnschr., 1912, **59**, 1437.

4. Kaplan, D. M.: Serology of Nervous and Mental Diseases, Philadelphia, W. B. Saunders Company, 1914, 346 pp.

5. Lange, C.: Was leistet die reine Liquordiagnostik bei der Diagnose des Hirntumors? Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1921, **33**, 582.

6. Lotmar, F.: Zur Kenntniss der Wassermann-Reaktion bei Tumoren des Zentralnervensystems, Schweiz. med. Wchnschr., 1921, **51**, 1013.

7. Moersch, F. P.: Serology in Brain Tumors, J. Nerv. and Ment. Dis., 1923, **58**, 16.

8. Morrison, A. W., and McKinley, J. C.: The Apparent Effect of Arsphenamin in Two Cases of Brain Tumor, J. Nerv. and Ment. Dis., 1924, **59**, 264.

9. Marburg, O.: Beitrag zur Frage der Kleinhirnbrückenwinkeltumoren, Neurol. Centralbl., 1910, **29**, 570.

10. Newmark, L.: The Occurrence of a Positive Wassermann Reaction in Two Cases of Nonspecific Tumor of the Central Nervous System, J. Am. Med. Assn., 1912, **58**, 11.

11. Noehte, J.: Ueber einen mit Salvarsan behandelten Fall von malignem Gehirntumor, München. med. Wchnschr., 1912, **59**, 529.

12. Nonne, M.: Zur Differentialdiagnose von syphilogener Erkrankung des Zentralnervensystems und nicht syphilogener Erkrankung desselben bei Syphilitischen, Neurol. Centralbl., 1910, **29**, 1178.

13. Nonne, M.: Syphilis und Nervensystem, 3d ed., Berlin, S. Karter, 1915, 902 pp.

14. Riggs, C. E.: Syphilitic Infections of the Central Nervous System, Canadian Med. Assn. J., 1914, **4**, 9.

15. Smith, J. C.: Tumor cerebri, Pleocytosis spinalis und die Eiweissverhältnisse der Spinalflüssigkeit, Deutsch. Ztschr. f. Nervenh., 1925–1926, **88**, 278.

16. Stern, F.: Ueber positive Wassermannreaktion bei nichtluetischen Hirnerkrankungen, Arch. f. Psychiat., 1920, **61**, 725.

A BRIEF DISCUSSION OF THALAMIC SYNDROME WITH A CASE REPORT.

By E. S. Gurdjian, M.D., Ph.D.,

ROCHESTER GENERAL HOSPITAL, ROCHESTER, N. Y.

The recognition of thalamic syndrome as a disease entity dates back to 1903 when Dejerine and Egger reported a case of thalamic disease. This was corroborated by autopsy findings. The following year Thomas and Chirey reported 2 cases of identical symp-

tomatology and for the first time proposed the use of the term: "Syndrome Thalamique." In 1907, Roussy reported his extensive experimental studies on the thalamus and discussed fully the thalamic syndrome. At that time, he defined the condition as follows:

Persistent superficial hemianesthesia, organic in type, more or less serious as concerns superficial sense (touch, pain and temperature) but always very pronounced as concerns deep sense; a slight hemiplegia usually without contractures and rapidly regressive; a slight hemiataxia and a more or less complete asterognosia; intense, persistent, paroxysmal and at times intolerable pains on the affected side, pains which are not relieved by narcotics; choreoathetotic movements in the extremities of the paralyzed side. This author speaks also of sphincter changes (vesical and rectal tenesmus), hemianopsia, etc., accompanying the syndrome and which are not necessarily characteristic of the same.

Before going into a more lengthy discussion of thalamic syndrome and its clinical varieties, we shall next present a case which was examined at Dr. Camp's Clinic, University of Michigan, and which is a very good example of the above-mentioned complex of symptoms.

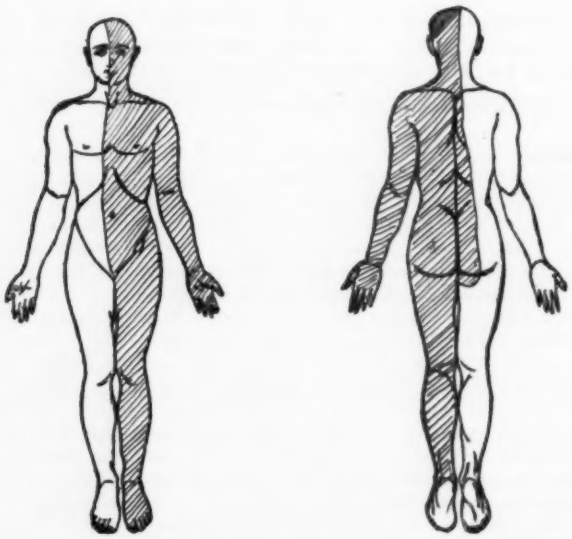
Case Report. Mrs. M. C. (Case No. 6650), aged thirty-four years, was referred to the Department of Neurology on May 19, 1925, with the chief complaint of peculiar feelings on the right side of the body. Her previous medical history was particularly suggestive of hemicrania attacks with vomiting. She had had three miscarriages; two preceded the birth of a child—at the time three years old—and one followed the latter normal delivery. Her blood Wassermann was negative.

Since the last miscarriage, she felt worse. Her present trouble began five days after her last confinement three years ago. She noticed a peculiar sensation down the right side of her body. She was totally unable to speak for about two hours, although she was fully conscious. She got up about ten days later and noticed a dragging of the right foot in walking. This dragging lasted for about a year. The whole right side felt as if it were asleep all the time. She also complained of spontaneous pains on the right side which were paroxysmal in nature. A month ago she had pains in the hip.

Examination showed that the patient was a well-nourished individual. She was of good color and there was no cyanosis noted. There were no differences in the lacrimation of the two sides, no flushing of the face, no unilateral sweating. The skin and appendages appeared normal. In smiling she drew back the left corner of the mouth much more than the right. She was able to close both eyes firmly and wrinkle both sides of the forehead. Masseters contracted firmly. The extraocular movements were normal. There were no nystagmus and no Argyll-Robertson pupil. The tongue was essentially negative. There were no enlarged glands in the neck. Tendon reflexes were practically normal. The grip was good in both hands, but on continued effort the grip of the right hand became weaker than the left (the patient was right-handed). No gross signs of ataxia were noted. She did not recognize a match in the right hand. A quarter was called a cent in the right hand. The different shapes of wooden blocks were recognized correctly and promptly. A light touch on the right side was registered as a painful stimulus. The difference in sensation between the two sides was plainer in the arms than it was in the trunk, however, the whole half of the body including an area of about an inch to the left of the midline was the site of a hypalgesia (see illus.). She seemed to

have some knowledge of sense of motion and position of the fingers but she was unable to fix the fingers in the left hand in the same position as those in the right, with the eyes closed. Deep pain and vibratory sense were considerably diminished in the right hand. She had a high blood-pressure but there were no other corroborative signs of chronic nephritis or heart disease.

Discussion. The history of this patient and the clinical data we have on the case are very characteristic of thalamic syndrome. The etiologic factor in this particular instance is most probably a vascular one—embolism of the arterial channels supplying the thalamus of the left side. The history and the clinical findings indicate a practically pure case of thalamic syndrome; most instances quoted in the literature consulted have an added symptomotology pathognomonic of extensive internal capsule involvement.



The most common etiologic factor in the production of Roussy's syndrome is vascular change in the thalamus. Most cases, however, occur among the older people (arteriosclerotic, chronic nephritic, chronic heart, luetic and so forth, cases), and it is rather surprising to find it in the relatively young. In the case quoted above, the patient dated her condition back to a miscarriage. At this time she may have had a thrombosis of the uterine vessels which could be followed by embolic and thrombotic changes in the different parts of the body. It is unfortunate that we do not have the exact history and the clinical data of her period of acute illness.

The possibility of complicating neural manifestations in thalamic syndrome becomes very evident when we consider the fact that the

disease is most often caused by vascular changes. These may involve not only the thalamus but also the perithalamic tissue. As a matter of course even the so-called pure cases have, at the onset, certain associated symptoms of involvement of the surrounding tissues, due possibly to the edema and swelling which in the course of time subside and the case becomes a more or less pure example of the disease. However, at times the hemorrhage is so extensive that there is permanent damage to the perithalamic tissues with consequent mixed clinical varieties as noted in the literature. Thus Roussy (1922) speaks of thalamopyramidal and thalamostriatal types where aside from the sensory changes (due to thalamic involvement), one also notes spasticity (pyramidal tract involvement) or muscular rigidity, intentional hypertonicity, and so forth (due to striatal involvement). L'Hermitte and Fumet (1922) speak of a pure case of hemalgesia characterized by excruciating pain involving one-half of the body, while other sensory manifestations were normal for all intents and purposes. Cases associated with choreoathetotic movements of the body were noted by Roussy (1907). Extensive involvement of thalamus has also been found to lead to abnormal eye manifestations (hemianopsia, and so forth). Of special interest are cases of bilateral involvement as reported by Christiansen (1920) and others. In these cases the sensory changes were noted all over the body.

The question of spontaneous pain in thalamic syndrome is of special importance. It would be very easy to mistake such a central pain with one caused by local factors in a given part of the body. For example, in the case above cited the pain in the hip could be taken for an arthritic manifestation and unnecessary treatment thus be instituted. The mechanism of production of such spontaneous pain is probably one of pressure against sensory incoming nerve fibers in the thalamus (the pressure, of course being caused by gliosis of the infarcted part).

The patient above cited did not have any sphincter changes (vesical or rectal). A good number of thalamic cases and others in which the basal ganglia are involved do present such clinical manifestations. Many such patients have been treated for local vesical or rectal disease without apparent amelioration of their condition.

In the typical case, the diagnosis of thalamic syndrome is not difficult. Careful neurologic examination and laboratory methods should rule out all conditions simulating this disease. Most of the borderline cases (those with extensive internal capsule involvement overshadowing the thalamic changes) could also be diagnosed if we keep in mind the possibility of the presence of thalamic syndrome.

The treatment of the condition is unsatisfactory. Large doses of potassium iodid are indicated. Treatment of the underlying factors in the production of the disease should also be tried.

I should like to express my indebtedness to Doctor Camp for permission to report the above case and for suggestions concerning the same.

REFERENCES.

Christiansen, V.: Syndrome thalamique double a evolution lents et progressive, Rev. Neurol., 1920, **36**, 793.

L'Hermitte and Fumet, C.: Syndrome hemialgique pur chez un lacunaire, Rev. Nurol., May, 1921, **37**, 468.

Klippel, M., and L'Hermitte, J.: Les syndrome sous-corticaux, in the Nouveau Traité de Medecine, edited by G. H. Roger, 1925.

Roussy, G.: La couche optique, Steinheil, Paris, 1907.

Roussy, G.: Les troubles sensitifs d'origine cérébrale. Questions neurologique d'actualité, Masson, 1922.

AN UNUSUAL CASE OF DIABETES MELLITUS: DEATH AFTER THIRTEEN YEARS' OBSERVATION; NECROPSY.

By A. H. Gordon, C. L. Connor,

and

I. M. Rabinowitch,

Montreal, Canada.

(From the Medical Service of A. H. Gordon, M.D., and the Departments of Pathology and Metabolism of the Montreal General Hospital.)

This case of diabetes mellitus is reported because of: (*a*) The long period of time the patient has been under observation; (*b*) the complete clinical and metabolism studies made; (*c*) the difficulties met with in the differential diagnosis in the last stages; (*d*) the fatal termination in spite of the use of enormous quantities of insulin; (*e*) the complete postmortem examination; (*f*) the lessons which it has taught. The history in chronologic order is as follows:

With the exception of scarlet fever and measles in childhood, this man was apparently perfectly well until 1903, when, at the age of thirty-five years, he contracted typhoid fever. The illness was complicated by an acute abdominal condition associated with pain over the liver region and accompanied by vomiting, and for which he was seen by A. T. Bazin, of the surgical staff, who regarded it as an attack of acute cholecystitis. He was apparently well after recovering from the typhoid fever, except that practically every three months thereafter, for about ten years (that is, until 1913), similar attacks of pain over the liver region would occur accompanied by vomiting. Early in 1913 he weighed 160 pounds. He then began losing weight, had great thirst and felt weak. He paid no particular attention to this for about four months. The condition did not, however, improve. He then consulted Dr. Bazin, who

found sugar in his urine, diagnosed the condition as diabetes mellitus, and referred him for treatment to one of us (A. H. G.).

The family history was negative, with the exception of the fact that one brother died in coma, the cause of which was unknown.

He was treated for the diabetes for about six years. The treatment was based upon the principle of undernutrition, and in January, 1919, he weighed 114 pounds, having lost 46 pounds. This weight was retained for some months, then again he began losing weight, and on April 14, was admitted for treatment (Hosp. No. 1937–19).

On admission he had large amounts of both sugar and acetone bodies in the urine, but no albumin. Again he was treated on the principle of undernutrition, and on June 1, 1919, he was discharged from the hospital. At that time, he weighed 107 pounds. The urine then contained no sugar nor acetone bodies, and there were no symptoms, with the exception of the emaciation, referable to the disease. His diet then consisted of carbohydrate, 55 gm.; protein, 97 gm.; fat, 85 gm.; a total of 1378 calories.

He was well for about a year, and then again (1920) noted frequency, and also complained that his eyesight was failing. His diet was readjusted, the urine rendered free of sugar, and his condition, though not entirely satisfactory, apparently remained unchanged, and he was not again admitted for observation until November 3, 1922 (Hosp. No. 5558). The purpose of this admission was to make a careful study of his metabolism prior to sending him to Toronto for insulin treatment. At this time none was available in Montreal.

During the routine examination the positive physical findings then were the marked absence of fat in the subcutaneous tissues and a low blood pressure (systolic 90 mm. Hg. and diastolic 65 mm. Hg.). In the right eye the retina was pale, and the disk was definitely whiter than usual. In the left eye, there was a slight degree of optic atrophy, but no apparent retinitis. The only other positive finding was the absence of the knee jerks. A summary of the metabolism findings was as follows:

On a diet consisting of 129 gm. of available glucose ($G = C + 0.1F + 0.58P$); the volume of urine for twenty-four hours was 2200 cc., containing 77 gm. sugar, and 2100 cc. tenth-normal organic acids, 21 gm. nitrogen, and 2.7 gm. ammonia. In the fasting state the blood-urea nitrogen was 21 mg. per 100 cc.; creatinin, 1.8 mg. per 100 cc. The blood sugar was 0.286 per cent; the plasma CO_2 combining power was 43 volumes per cent. The respiratory quotient in the fasting state was 0.740. The note then made was as follows:

The total glucose intake calculated from the total metabolism carbohydrates, fat and protein, to meet the caloric requirement was 129 gm. Since the total amount of sugar excreted was 77 gm., the glucose tolerance, including that available from carbohydrate, fat

and protein, was 52 gm. This indicates severe diabetes. The respiratory quotient also suggests severe diabetes. At that time he weighed 97½ pounds.

He was next seen March 29, 1923, when he weighed 126 pounds, thus having gained about 28 pounds in approximately five months. At this time his urine was free from sugar and acetone bodies and the blood sugar was normal (0.081 per cent). He stated that the diet he was given at Toronto, and which he was following consisted of: Carbohydrate, 48 gm.; fat, 193 gm.; protein, 79 gm. With this diet he was taking 37 units of insulin a day—22 units before breakfast and 15 units before the evening meal. Clinically he appeared to be very well and he felt very well.

He was again seen on April 5, and at this time he weighted 131 pounds; the urine was free from sugar and acetone bodies and the blood sugar was 0.25 per cent in the fasting state. The data obtained during subsequent visits until the end of 1926, are recorded in the following table:

Date.	Weight pounds.	Urine.			Blood, per cent.	
		Sugar.	Acetone bodies.	Albumin.	Sugar.	Cholesterol.
November 3, 1922 . .	97.5	+	+	0	0.286	
March 29, 1923 . .	126.0	0	0	0	0.081	
April 5, 1923 . .	131.0	0	0	0	0.250	
August 4, 1924 . .	133.0	0	0	0	0.250	
March 3, 1924 . .	140.0	0	0	0	0.263	
March 6, 1925 . .	158.0	0	0	0	0.245	0.312
May 5, 1926 . .	164.0	0	0	0	0.235	0.331
January 28, 1927 . .	174.0	0	0	0	0.273	0.483

He continually felt well, appeared to be very well, and his weight was gradually increasing. Some idea of this may be gained from the accompanying photographs of the patient, one taken in November of 1922 and again in August of 1924 (Fig. 1). There were, however, disturbing features, namely, a high renal threshold for sugar (a persistent hyperglycemia greater than 0.18 per cent in the absence of glycosuria) and an increasing hypercholesterolemia.

On January 28, 1927, he weighed 174 pounds, the urine was free from sugar and acetone bodies, the blood sugar was 0.273 per cent, and the plasma cholesterol 0.483 per cent.

His skin at all times had a peculiar yellow appearance and was edematous. Much of this body weight was attributed to the retention of water which is commonly seen after insulin treatment, and which for the want of a better name is now called insulin edema.

In view of the findings during his last visit, he was advised to increase the amount of insulin. This he did. On February 20, he was admitted to the Montreal General Hospital in deep coma.

The history of events since his last visit (January 28, 1927) obtained from his wife was as follows:

Since February 10, he had not felt well, complaining continually of "gas in his stomach" after meals. At 3.30 P.M. on February 18th, he commenced to vomit. This continued throughout the night. The following morning he became very thirsty, drank large quantities of water, but these were not retained. He called in a physician who gave him some powder to stop the vomiting. At 4 A.M. on February 20th, his wife found him in a very deep sleep, and believing that his breathing was not normal, tried to arouse him, which she failed to do. One of us (I. M. R.) was then notified of his condition. Fifty units of insulin were given subcutaneously and he was sent to the hospital.

FIG. 1.—Showing general condition of November, 1922, compared with that of August, 1924.

On admission, at 6.50 A.M. of the same day, the patient was, obviously, in deep coma. The insulin given had, apparently, no effect. The face was flushed, and the respirations were markedly of the Kussmaul type. The tongue was dry and yielded the characteristic "sand-paper" like sensation on palpation. There was a marked acetone odor to the breath. The eyeballs were not only soft, but could just be felt as small masses deep in the orbital fossæ. The pulse was regular in rate and rhythm and had a good volume; temperature was 99.2° F. A specimen of blood was obtained, and also a specimen of urine by catheterization. The blood sugar was 0.820 per cent, and the urine showed large amounts of sugar, acetone bodies, a trace of albumin and a shower of casts. He was given 100 units of insulin subcutaneously.

At 9 A.M. he was still in deep coma and there appeared to be no

improvement. The pulse was still regular and of good volume, and there was no alteration either of the color or respirations. At this time, the blood sugar was 1 per cent, and the white-cell count was 18,400. Because of the above findings he was given 50 units of insulin intravenously.

At 9.40 A.M. there appeared to be some evidence of recovery; there was a slight movement of the eyelids, hands and feet. There was, however, no alteration in the type of respiration, in the color nor in the pulse.

At 11 A.M. the blood sugar was still 1 per cent. At this time it was possible to obtain only 5 cc. of urine by catheterization. This specimen still showed sugar, but only a trace of acetone bodies, many more casts, and a much heavier trace of albumin. The patient was obviously becoming anuric.

At 12.30 P.M. he was still in very deep coma. There was now evidence of failing circulation. The pulse was very rapid, and the tension was low, but it was still regular in rate and rhythm. There was some cyanosis of the finger nails. He was now given 100 units of insulin intravenously, and one ampule of caffein sodium benzoate was ordered to be given every four hours.

At 3 P.M. he was seen by L. C. Montgomery. At this time the respirations were stertorous, and slightly Cheyne-Stokes in type. The condition of the pulse was still the same. The pupils were contracted and fixed. The heart sounds were very distant; there were no adventitious sounds. The patient was in deep coma and could not be roused. The upper and lower limbs were flaccid, but the right side was perhaps slightly more so than the left. At times, there were very slight movements of the left hand and foot. There was a suggestive positive Babinski sign on the right side, but definitely positive on the left. The skin was moist and the extremities were cold. Dr. Montgomery's impression at that time was that besides the diabetic coma there was possibly a pontine hemorrhage. A lumbar puncture was suggested. This was done. The findings were entirely negative.

At 4 P.M. the blood sugar was 0.78 per cent, and the coma had deepened. The pulse was very rapid and weak. He was given 100 units of insulin intravenously. At 4.30 P.M. he was again seen by Dr. Montgomery. The new findings were numerous râles at both bases of the lungs. No reflexes could now be elicited. The Babinski had disappeared. At 4.45 P.M. the breathing became very shallow and the cyanosis marked. This condition remained unchanged until 6.10 P.M., when he died.

On examination of the blood obtained from the heart about five minutes postmortem the following were the findings: Sugar, 0.924 per cent; urea nitrogen, 101 mg. per 100 cc.; creatinin, 4.0 mg. per 100 cc.; diazo color reaction for uremia, positive.

A summary of the relevant postmortem findings follows:

The skin was yellow in color, and the subcutaneous tissues edematous. There was very little fat anywhere.

The gall bladder was embedded in a mass of adhesions involving the pyloric end of the stomach, the first part of the duodenum, the omentum and the hepatic flexure of the colon. When dissected out, it was found to be contracted down over one soft gall stone. The walls were thickened and fibrosed, and on the inner surface there was a small firm papillomatous outgrowth. The cystic duct was replaced by a fibrous-tissue cord; the common, hepatic, and pancreatic ducts were patent, and showed no sign of recent infection, but these were dissected with difficulty, due to the old adhesions around them.

Microscopically, the gall bladder contained a great deal of fibrous tissue, which replaced the muscle in places. The epithelium was very hyperplastic in one section, and in others there were numerous glands buried deep in the wall. An occasional lymphocyte could be found in all layers.

The pancreas weighed 70 gm. and from palpation and inspection of the cut surfaces it could not be said that there was any increase of fibrous tissue. It was most remarkable for the small number of islets. Eighteen sections were taken from the head, body and tail. In some of these sections no islets could be recognized, and nothing that indicated where there might previously have been any. In two sections a few small collections of cells which differed somewhat from the acinar cells were seen, incompletely surrounded by capillary vessels. In the same and in a few additional sections (Fig. 2) very small masses of hyaline material were found, which presumably represent changed islets. Even these were very few, and were found only after some search. There was moderate fibrosis in some places. This was more of an interacinar infiltration. The pancreatic ducts and branches had somewhat thickened, fibrosed walls, but there was scarcely more interlobular fibrous tissue than usual (Fig. 3). Many of the small arteries had thickened hyaline walls, some to the extent of causing almost complete occlusion of the lumen. The larger arteries showed intimal thickening varying from slight to marked.

Equally interesting as the findings in the pancreas were those in the bloodvessels, particularly those of the base of the brain. The vertebral arteries contained large golden yellow nodules. The arteries of the circle of Willis were beaded and firm and resembled the usual severe arteriosclerosis except for the bright yellow color.

Sections from the vertebral, basilar and internal carotid arteries showed marked fatty infiltration. The lumina of some of the vessels were narrowed by the thickened intima, and the large fatty cells beneath it. The media of some of the vessels were almost completely replaced by calcium and fat. Scharlach R stain showed large globules of fat in the media and between the media and adventitia, as well as beneath the intima (Fig. 4).

The aorta showed marked fatty changes beneath the intima, and irregular thickening, by fibrosis, of the intima. In places the media was encroached upon by fat-laden cells, and small amounts of calcium were present between intima and media. The process did not differ from the usual rather far-advanced arteriosclerosis.

In a section of the femoral artery the arteriosclerosis corresponded to the peripheral arteriosclerosis known as the Mönckeberg type.

Chemical analyses of the bright yellow portions of the vessels suggested the presence of vegetable lipochromes in that they had high cholesterol contents and the material colored blue with concentrated sulphuric acid and green with a potassium iodid and iodin solution.

The heart weighed 420 gm. There was thickening and fatty degeneration of the aortic leaflets of the mitral valve and sinuses of Valsalva. There were some atheromatous plaques in the pulmonary artery and an increase in epicardial fat. The consistency of the muscle was rather softer than usual. The coronary orifices were patent, but the arteries were markedly sclerosed.

Microscopically, the heart muscle showed moderate fragmentation but the striations were well preserved, and no degenerative changes were evident. No scars were present, but there was a definite interstitial edema. The epicardium and endocardium were normal in appearance. A section of coronary artery showed moderate intimal thickening, and marked fatty infiltration beneath the intima. Many large fat-laden cells were present, partly encroaching upon the media of the vessel.

In the kidneys, a few small scars involving three to five glomeruli were present beneath the capsule. The glomeruli showed no infectious changes, old or recent. The glomerular capillaries, and some of the glomerular capsules showed slight thickening and hyalinization. The afferent (or efferent, or both) arterioles also showed this hyaline change. Many of the larger arteries had a thickened fibrosed intima. The cells of the convoluted tubules were greatly swollen, and in some tubules the lumina were almost occluded. The cells contained numerous small vacuoles, and an occasional nucleus was vacuolated. These vacuoles were seen to represent glycogen in carmine-stained sections; some of them, however, were due to the presence of fat, as shown by Scharlach R preparations. Swelling and vacuolization of the cells of Henle's tubules were present also.

The liver weighed 1920 gm. The cells showed marked vacuolization. Some contained large vacuoles which were obviously fat, but most cells contain several (from 5 to 20) small or moderate sized vacuoles which with carmine stain proved to be glycogen. The cytoplasm outside the vacuoles was granular, and some cells contained small amounts of yellow pigment. No degenerative changes were evident, and there was no infectious lesion. The

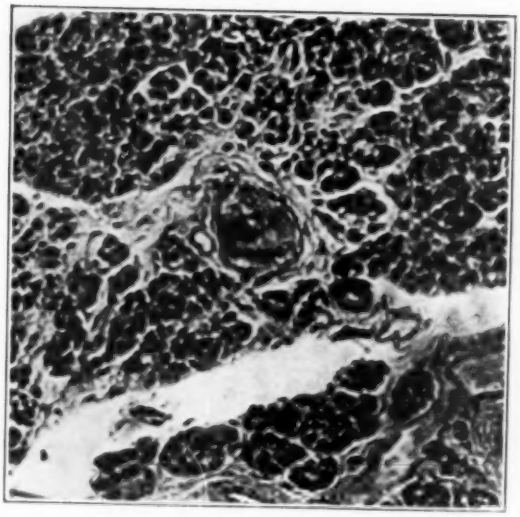


FIG. 2.—One of the few hyalin islets of the pancreas. (× 100.)

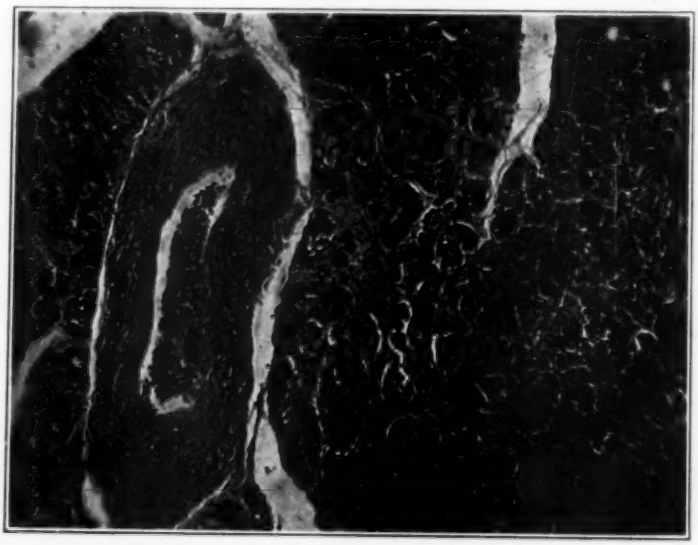


FIG. 3.—Moderate interlobular and interacinar fibrosis throughout. (× 80.)

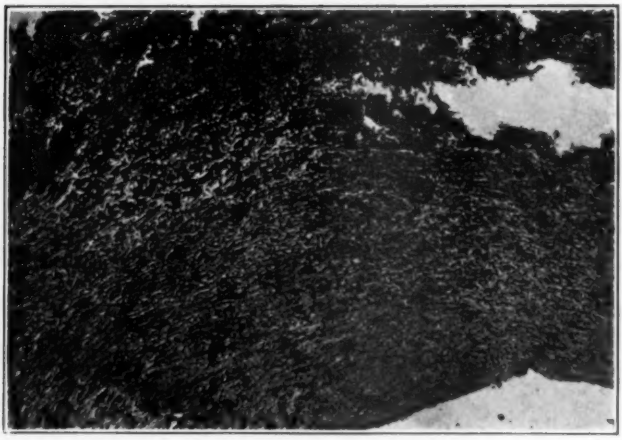


FIG. 4.—Section of vertebral artery stained with Scharlach R. The black masses are fat in the intima and media. (× 50.)

FIG. 5.—Degeneration of epithelium of convoluted and Henle's tubules in the kidney. (× 800.)

portal canals were narrow, and contained little fibrous tissue and few cells. The bile ducts showed no acute or chronic lesion.

The remainder of the anatomic findings, with one exception, were of no particular interest, and for purposes of brevity are omitted. There was no infectious lesion found, and no hemorrhage of the brain. The exception was the general edema of all tissues. This phenomenon will be referred to again.

Discussion. The first impression was that we had an individual who, because of typhoid fever, developed cholecystitis, and that repeated attacks of the latter led to a chronic pancreatitis, and progressive destruction of the pancreas resulted in diabetes. Because of the progressive destruction of the pancreas, undernutrition treatment failed in time, and for the same reason insulin eventually failed to control the disease. These observations proved, on post-mortem examination, to be only partly correct, in that cholecystitis was found, and also that the diabetes was of pancreatic origin, but it will be noted from the anatomic findings, there was little evidence of pancreatitis. The lesson this teaches is that in spite of a very clear history, it does not necessarily follow that diabetes, following repeated attacks of gall-bladder disease, is due to chronic pancreatitis. This may, at times, explain the lack of improvement in the diabetic condition in some patients with gall-bladder disease when operated upon for that purpose.

In this case we have also a demonstration of the fact, repeatedly emphasized in this clinic, that the clinical picture, that is, the attitude, expression, color, nutrition, and so forth, is not a reliable index of progress in insulin treated diabetics. Blood analyses are indispensable here.

The findings also suggest the prognostic significance of the cholesterol content of the blood, and also strengthen the view, not universally accepted, but repeatedly emphasized in this clinic, that hyperglycemia indicates active diabetes, whether the individual has or has not sugar in the urine. This patient had no sugar in the urine since March, 1923, in spite of the marked degree of glycemia. There are three possible explanations of this in this case, namely, chronic diabetes, arteriosclerosis and insulin. That the latter may be responsible for a high renal threshold for sugar has recently been suggested.[1]

The edema deserves special mention. Insulin produces an edema of the tissues of the diabetic, and this largely accounts, in a great number of cases, for the rapid increase of body weight frequently noted. Little literature has appeared on this subject, and the mechanism of its production is not understood. It has been shown by one of us[2] that it is apparently not due to the usual causes met with prior to the days of insulin, namely, cachexia, dietetic alterations, ingestion of large quantities of table salt and sodium bicarbonate administration, and is apparently not due to

kidney damage. That it is due to insulin directly can readily be demonstrated, since if insulin is discontinued for a few days, polyuria results, and this parallels, approximately, the rapid losses of body weight. Differing from active diabetes, the polyuria is not, as a rule, accompanied by glycosuria. The edema appears to be related to the dosage of insulin. It is interesting to note that as we have found a suggestive relationship between insulin dosage and edema[2] so has Joslin found such a relationship between insulin dosage and anuria.[3] This patient also had anuria.

From the blood findings shown above (urea, creatinine, and diazo-color reaction), it is obvious that this patient also had uremia. He had no demonstrable chronic nephritis during life. At his last visit to the clinic, January 28, 1917, he had no albuminuria. The post-mortem findings showed some arteriosclerotic changes, and the usual tubular degeneration associated with diabetic acidosis (Fig. 5.) That diabetics in coma may have urem..., regardless of whether they have or have not had nephritis prior to the onset of the coma, is generally known. The recognition of this fact is important because it may, as it has in this case, by its cerebral manifestations, complicate the clinical diagnosis. The pupillary findings, muscular twitchings and the alteration of the reflexes may suggest hemorrhage, which they did in this case. Hemorrhage was further suggested by the slight fever and the leukocytosis. The fever in this case was probably due to the uremia and the leukocytosis to the diabetic coma. That diabetics may, while in coma, have marked degrees of leukocytosis is probably not known as generally as it might be. Cell counts of 15,000 and 25,000 are commonly met with in adults, and counts of 35,000 and upward are not rare in children.

It is difficult to explain the failure of the insulin to influence the course of the diabetes. The patient did not have any of the usual conditions, such as infections, and so forth, which are known to counteract the effects of insulin. Certain possible explanations are suggested. Past experience suggests that fever and leukocytosis interfere with the action of insulin, regardless of the causes of their production, and this patient had both fever and leukocytosis though no infection. These may have been responsible factors. On the other hand, the edema may have been responsible in that the colloids of the edematous fluids may have absorbed the insulin when it was given subcutaneously, thus interfering with its reaching the necessary site of action, wherever that may be. This would not, however, explain its failure to act when given intravenously. Another possible explanation is that the uremia, probably aggravated by the large doses of insulin, may have caused irritation of the Claude Bernard center of the brain, interfering with glycogenesis which is now generally regarded as a necessary preliminary to oxidation of glucose. This suggestion is made in view of Joslin's recent observations on the relationship between insulin dosage and anuria.[3] These are, however, only suggestions. An interesting observation is that,

as far as could be discovered from the literature, this is the first case recorded in the literature of the blood of a diabetic in coma having a positive diazo-color reaction.

Summary. A case of diabetes mellitus is reported. The patient was under observation for thirteen years, during which time complete records of clinical and metabolism findings were kept. This case demonstrates that, in spite of a very clear history, it does not necessarily follow that diabetes following repeated attacks of gall-bladder disease is due to the latter. This may explain the failures at times of surgery to alleviate or improve diabetes when associated with disease of the biliary passages. This case also emphasizes the fact that the clinical picture (the attitude, expression, color, nutrition etc.,) is not a reliable index of progress of insulin-treated diabetics. Blood analyses are here indispensable. This patient appeared to be well nourished and felt well. The postmortem findings, however, showed that the skin did not contain fat, but water. Also because of the long duration of the disease and the arterioscleorsis, other evidence of active diabetes (glycosuria) was masked. The patient had a raised renal threshold for sugar. This case is also another demonstration of the relationship between the cholesterol content of the blood and prognosis.

The differential diagnosis during the final stages of the disease was difficult, because of a combination of findings not uncommon but not frequently mentioned in the literature. Cerebral manifestations of diabetic coma may simulate those of uremia or cerebral hemorrhage. Suppression of urine, albumin and casts, high blood urea and creatinin, leukocytosis, altered reflexes and fever were all present in this case.

Other clinical features of interest were the presence of insulin edema, the color of the skin and the absence of response to insulin.

The pancreas and the bloodvessels of the brain were the organs of special interest postmortem.

BIBLIOGRAPHY

1. Rabinowitch, I. M.: Brit. J. Path., 1926, **7**, 352.
2. Rabinowitch, I. M.: Canada Med. Assn. J., 1927, **17**, 685.
3. Joslin, E. P.: Med. Clin. North America, 1927, **10**, 1281.

CAROTINEMIA.

By Willard C. Stoner, M.D.,
ST. LUKE'S HOSPITAL, CLEVELAND.

The study of the various manifestations of jaundice and skin pigmentations has always been a subject of great clinical interest. In recent time, a renewed interest in the subject has resulted from the recognition of certain skin pigmentations being due to ingested

pigments contained in food which are deposited in the tissues, notably the skin. There are so-called carotinoid coloring matters which have been designated the lipochromes contained in substances such as milk fat, egg yolk, body fat and in certain vegetables such as carrots, green vegetables and oranges. Not until comparatively recently have such coloring matters been recognized as being responsible for body tissue discoloration, notably the skin.

A number of cases designated carotinemia were described by German authors subsequent to the war which obviously occurred incident to the high vegetable diet at that period. These cases occurred more commonly in children, where exclusively vegetable diets were given, rich in carrots and other green vegetables. Hess and Myers[1] in 1919 were the first to give an extensive description of this condition in the American literature. They described this peculiar skin pigmentation under the term "carotinemia" and regarded it as a new clinical condition. A similar condition was described by German authors a few years previous under the term "pseudoicterus" and they called attention to the possibility of confusion with true icterus, the chief difference being the absence of pigmentation of the sclera in pseudoicterus or carotinemia.

As early as 1904, von Noorden[2] discussed under the heading "xanthosis diabetica" a discoloration of the epidermis, a canary-yellow color affecting more particularly the palms of the hands and soles of the feet in diabetics who were maintained on a high vegetable diet. Moro,[3] in 1908, discussed a subicteric appearance of the skin in nurslings who were fed carrot soup in conjunction with milk feeding. Van den Bergh,[4] in 1913, discussed various pigments found in human blood serum and noted high lipochrome content in the blood serum of diabetic patients. He described a peculiar orange-yellow skin unassociated with discoloring of the scleræ. This xanthotic pigmentation was found spectroscopically to be the same as the coloring matter of carrots. Kaupe,[5] in 1919, observed nurslings with this peculiar skin discoloration affecting most markedly the cheeks, the alæ nasi and the forehead. He described the discoloration as being more of a lemon-yellow than true jaundice and found that the condition disappeared quickly when the high carrot diet was withheld. He reported that the literature did not give description of a similar condition and that such a clinical picture might be mistaken for some other pathologic condition. Stoeltzner,[6] a little later in 1919 in commenting on Kaupe's discussion, stated that he had observed a similar clinical condition in children over a period of years and that the number of cases had greatly increased incident to the World War period. He called it pseudojaundice and thought that a high tomato diet might give a similar pigmentation, stating that the yellow-red color of the tomato, lycopin, is chemically related to carotin. Lycopin in small quantity is also found in the carrot. These observations were all made on

nurslings and children. Klose[7] observed that only a small percentage of children fed on a high carrot diet developed carotinemia and recognized that it occurred more commonly in the obese child. It is a lipoid-soluble coloring matter contained in carrots and, therefore, he advanced the idea that there is probably some connection with fat metabolism. Inasmuch as the pigment is more marked over the exposed surfaces of the body, he concluded that the light intensified this pigmentation.

Salomon,[8] in 1919, stated that pseudojaundice in children after the ingestion of carrots corresponds absolutely to the xanthosis described by von Noorden in 1904. Schüssler,[9] in 1919, described 3 cases of carotinemia occurring in adults, aged fifty-four, sixty-three and sixty-eight years, respectively. The two eldest showed senile changes and the youngest was a strong healthy man. All 3 cases stated that owing to lack of potatoes they had lived on carrots chiefly. Two of the cases had recognized that the discoloration came gradually while the other had not observed it at all. Moro[10] stated in 1919, that he had observed a similar phenomenon in nurslings in 1908 and had reported the same to the Munich Pediatric Society. Bürger[11] reported that there was a definite parallel between the degree of xanthosis and the amount of lipochrome in the blood and that both could be influenced by diet. Chemical and spectroscopic tests showed the lipochrome to correspond to the carotinoid group of pigments which are closely associated with the chlorophyl of green plants.

Van den Bergh[12] found by feeding a diet rich in green leafy vegetables and eggs there was a definite increase in the lipochrome in the blood serum which under normal conditions is small and variable. He found an increase of lipochrome in the diabetic and where xanthosis was present there was a definite increase of carotin. They found that the lipochrome content of the various organs such as the suprarenal glands, liver and spleen, were not in relation to the blood-serum content. The suprarenal glands were found very rich in lipochrome, therefore, they regarded the organ content not in relation to any disease. Ryhiner[13] found poorly nourished infants more commonly affected, contrary to other observers. He found it after the ingestion of eggs. Hess and Myers reported it after the ingestion of spinach and oranges. They observed a red tinge in the urine and serum after the ingestion of beets but no skin discoloration was apparent. Stoeltzner thinks that there is a chemical disposition of the skin for pigment absorption. The age range has been found to be from eight months to two years. The yellow pigment circulating in the blood of pernicious anemia is not carotin.

Palmer and Eckles[14] have carried out studies as to the relation of fodder to the carotin content of the tissues. Green feed greatly increases the color of the butter fat of cows chiefly because they contain carotin which accompanies chlorophyl of plants. Body

fat, blood serum, corpus luteum all depend upon the food pigment for intensity of color. No doubt these pigments not uncommonly cause skin discolorations which are not recognized as they are common in vegetable diet, egg yolk, etc. A diet rich in oranges may cause this discoloration. It is probable that the sallow yellow appearance of certain individuals at certain times commonly regarded as liver derangement may be due to these pigments. It is obvious that these pigments must alter the color of urine at certain times. Head and Johnson[15] in 1921 reported a case of carotinemia in an adult, a diabetic, which is comparable to the clinical picture of the patient studied by the author and incorporated in this report. They found, as other observers, that the yellow pigment, carotin, was not confined to carrots but that it included xanthophylls under the general term carotinoids, which are widely distributed in Nature and can be separated on the basis of solubility. Palmer and his associates have been able to produce an almost colorless milk fat or egg yolks by feeding a diet poor in pigments. Fat is the storehouse of carotinoids and the absence of these pigments accounts for the colorless fat of swine, sheep and goats. There is a wide variation among species in their behavior toward these pigments. These pigments are apparently harmless and have no useful bodily function.

Case Report. A case studied by the author is of sufficient interest to warrant a detailed report inasmuch as a previous diagnosis of jaundice had been made. Mrs. E. R., white female, aged sixty-five years, was admitted to the medical service of St. Luke's Hospital, March 5, 1927. Her chief complaint on admission was that of epigastric distress and an intense yellow discoloration of the skin. She had noticed that her skin was turning yellow as early as the preceding November. This was especially apparent on her hands. As for her gastric symptoms, the eructations of gas had been present over a long period of years and the occasional "soreness" in the epigastrium dated back five years. These symptoms had never before assumed the proportions of a complaint until she noticed the discoloration of her skin. She complained of constipation which had been present over a period of years. She did not give history of weight loss. With the exception of the usual childhood diseases, infrequent head colds and tonsillitis, the patient had always been quite well. She did not give history of jaundice. Family history has no bearing on the clinical condition. Menstrual and marital history are essentially negative.

Physical Examination. The patient is of slight build and rather undernourished but not asthenic. There is a slight generalized yellowish pigmentation over the whole skin surface with greater intensity on the palms of the hands and soles of the feet. She did not complain of pruritus as is always present in jaundice. She is distinctly the nervous type with choreiform movements, ticlike in character. The skull, ears and nose are negative. The scleræ are not icteric. The pupils are equal, regular and react promptly to light and accommodation. The extraocular movements are normal. There is no ptosis, nystagmus nor exophthalmos. The pharynx, tonsils and pillars are not abnormal. The tongue seems slightly smoothed out. The teeth are absent. The thyroid is not palpable. The breasts are

small and atrophic. The costal angle is acute. The left margin retracts slightly upon deep inspiration. The lungs are negative. The heart is negative. Blood pressure 120 systolic and 70 diastolic. There is no bradycardia. The abdomen is symmetrical and scaphoid. There is no spasm, tenderness or tumor and no sign of fluid is present. The liver, spleen and kidneys are nonpalpable. The extremities show no tremor, clubbing, cyanosis or edema. There is a slight hypertrophic change at the interphalangeal joints of the fingers. There is a slight shotty adenitis in the cervical and inguinal regions. The epitrochlear glands are not palpable. All reflexes are normal.

The patient was in the hospital for eight days during which time the temperature was normal, the pulse varied slightly over 80, and the respiration was 20. Dr. R. E. Barney of the dermatological department saw the patient in consultation and suggested carotinemia. A further history of the patient's habits of eating was then taken and it was found that she had been living for some time with an old bachelor brother who from habits of rigid frugality and preference had forced her to subsist almost exclusively on vegetables and carrots over a period of months during which time the peculiar skin condition developed.

Laboratory Examination. Several urine analyses were absolutely negative. No test for carotin in urine was made. The blood showed a hemoglobin of 85 per cent, white blood cells, 4550; red blood cells, 4,576,000. Differential count showed polymorphonuclears, 71 per cent; large lymphocytes, 11 per cent; small lymphocytes, 11 per cent; transitional cells, 7 per cent; no eosinophilic polymorphonuclears, no abnormal forms and morphology of red blood cells good. Occult blood was found in the feces but enemas were given and slight hemorrhoids were present. Blood sugar on fasting stomach was normal and the glucose-tolerance curve was likewise normal. The fragility of the red blood cells was not increased. Bile was present in the feces. Gastric contents showed a total acidity of 30, free hydrochloric acid, 16; combined hydrochloric, 5; no lactic acid, bile or occult blood was present. The Lyon-Meltzer test showed the typical three colored specimen. Fifteen hours after the administration of the Graham dye an indefinite gall-bladder shadow of uniform density was shown which was found quite definite seventeen hours after the administration of the dye. The behavior was physiologic.

The test for carotin in the blood was distinctly positive. The technique of the test which was used is as follows: Clear serum is mixed with an excess of plaster-of-Paris. The damp powder is transferred to a flask, alcohol added equal to the volume of serum and thoroughly mixed with the plaster-of-Paris mass. An equal volume of low-boiling petroleum ether is now added and vigorously shaken with the mass. On standing, the petroleum ether rises to the surface, giving an almost quantitative extraction of the carotin.

The test depends upon the fact that carotin forms well-colored solutions in ether, chloroform, petroleum ether, benzine, carbon tetrachlorid, and carbon disulphid, as well as in ethereal and fatty oils and oleic acid. Ordinarily carotin, when present in the blood, seems to be held in some sort of physicochemical combination with a fraction of the albumin in colloidal solution in the blood; while in some diabetics and others where the diet is rich in lipochrome-containing foods this combination apparently does not occur for the carotin can be extracted directly by shaking the serum with any of the preceding solvents. Where the combination does occur, direct extraction is impossible. However, if the serum is first treated with an equal volume of alcohol, the carotin can be readily extracted by shaking with the solvents mentioned.

Summary. In a carefully studied case of carotinemia in an adult the pigment has been demonstrated in the blood serum. A study of the medical literature has shown the condition to be relatively uncommon in adults, but common in nurslings and children where high vegetable diets have been given. The skin discoloration disappears on withdrawal of dietary rich in carotinoids. The condition is unassociated with disturbing symptoms and is of particular interest only from the standpoint of differential diagnosis. It has been confused with true jaundice and vague liver trouble.

I am indebted to Dr. Elizabeth C. Smith, of Warren, O., for having referred the patient to me for study.

BIBLIOGRAPHY.

1. Hess, A. F., and Myers, V. C.: J. Am. Med. Assn., 1919, **73**, 1743.
2. Von Noorden, C.: Die Zuckerkrankheit, ed. 4, Berlin, A. Hirschwald, 1907, p. 149.
3. Moro, E.: Karottensuppe bei Ernährungsstörungen der Säuglinge, München. med. Wchnschr., 1908, **55**, 1637.
4. Van den Bergh, A. A. H., and Snapper: Die Farbstoffe des Blutserums, Deutsch. Arch. f. klin. Med., 1913, **110**, 540.
5. Kaupe, W.: Hautverfärbung bei Säuglingen und Kleinkindern infolge der Nahrung, München. med. Wchnschr., 1919, **66**, 330.
6. Stoeltzner, W.: Ueber Pseudoikterus nach Mohrrübengenuss, München. med. Wchnschr., 1919, **66**, 419.
7. Klose, E.: Hautverfärbung bie Säuglingen und Kleinkindern infolge der Nahrung, München. med. Wchnschr., 1919, **66**, 419.
8. Salomon, H.: Ueber Pseudoikterus nach Mohrrübengenuss, München. med. Wchnschr., 1919, **66**, 564.
9. Schüssler: Ueber Hautverfärbung durch Mohrrübengenuss, München. med. Wchnschr., 1919, **66**, 596.
10. Moro, E.: Ueber Hautverfärbung durch Mohrrübengenuss, München. med. Wchnschr., 1919, **66**, 674.
11. Bürger, M., and Reinhart, A.: Ueber die Genese der Xanthose diabetica, Deutsch. med. Wchnschr., 1919, **45**, 430.
12. Van den Bergh, A. A. H., and Müller, P.: Das lipochrome Pigment in Blutserum and Organen, Xanthosis, Hyperlipochromämie, Biochem. Ztschr., 1920, **108**, 279.
13. Ryhiner, P.: Pseudoikterus bei Säuglingen und Kleinkindern nach carotinoidreicher Nahrung, Jahrb. f. Kinderheilk., 1921, **94**, 225.
14. Palmer, L. S., and Eckles, C. H.: J. Biol. Chem., 1914, **17**, 191, 211, 223, 237, 245; 1915, **23**, 261; 1916, **27**, 27.
15. Head, Geo. D., and Johnson, Ruben A.: Arch. Int. Med., 1921, **28**, 268.
16. Van den Bergh, A. A. H., Müller, P., and Broekmeyer, J.: Het lipochrome Pigment van Bloedserum en Organen, Xanthosis, Hyperlipochromæmie, Nederl. Tijdschr. v. Geneesk, 1920, **64**, 127.
17. Umber: Diabetische Xanthose, Berl. klin. Wchnschr., 1916, **53**, 879.
18. Von Noorden: Internat. Dermatologenkongress, 1904.
19. Hymans, van der Bergh and Snapper: Die Farbstoff des Blutserums, Deutsch. Arch. f. klin. Med., 1913, **110**, 540.
20. Wells, H. G., and Hedenburgh, O. F.: J. Biol. Chem., 1916, **27**, 213.
21. Editorial: J. Am. Med. Assn., 1920, **74**, 32.
22. Greene, C. H., and Blackford, L. M.: Med. Clin. North America, 1926, **10**, 733.
23. Mijake, I.: Arch. f. Dermat. u. Syph., 1924, **147**, 184, abst. J. Am. Med. Assn., 1924, **83**, 481.
24. Niehaus, F. W.: J. Am. Med. Assn., 1924, **82**, 547.
25. McGill, C.: J. Am. Med. Assn., 1922, **78**, 281.
26. Myers and Wardell: J. Biol. Chem., 1918, **36**, 147.
27. Willstatter and Mieg: Ann. d. Chem., 1907, **355**, 1.

THE USE OF DEXTROSE IN THE TREATMENT OF OBESITY.*

With Special Reference to the Reduction of the Body Weight without Markedly Lowering the Daily Caloric Intake.†

By Burgess Gordon, M.D.,

and

E. von Stanley, B.S.,

Philadelphia.

(From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital.)

Various dietetic regimes have been advocated for the treatment of obesity. Those of Banting, Oertel, Schweninger and von Noorden have been reviewed by C. Howard.[1] Recently the plan of Williams[2] has attracted attention, also that of Mason[3] which incorporates thyroid extract with a low-caloric diet. The effectiveness of these or similar diets depends perhaps on certain underlying causes of obesity. Apart from the endogenous type, however, which in certain instances is attributed quite definitely to glandular dysfunction and the so-called exogenous type which is due apparently to overeating, with insufficient exercise, little is known about the causes for obesity. For that matter, as Du Bois[4] has stated, "there is no stranger phenomenon than the maintenance of a constant body weight under marked variation in bodily activity and food consumption." It is no wonder that a solution for the cause of obesity has been delayed because so little scientific knowledge is at hand to explain the maintenance of the normal weight.

In general, the treatment of the exogenous type of obesity has been more or less haphazard. It has depended largely upon a reduced caloric intake with increased exercise. The chief causes for failure no doubt have been due to hunger, weakness and lack of courage to follow a restricted diet. The ill effects have been due perhaps to various metabolic and nervous disturbances and a lowering of resistance to infection.

These have led to the consideration of a regime which, if effective, would influence the weight and yet cause no untoward symptoms. The regime proposed for the present investigation is based essen-

* The expenses for this investigation were defrayed by grants from the E. T Bedford Fund for Research in Carbohydrate Metabolism and from Mrs. Howard A. Davis, of Philadelphia.

† (Read before the Interurban Club, Philadelphia, December 2, 1927.)

tially on a hypothesis, certain features of which may be considered without undue speculation. A condition of hypoglycemia in certain individuals may exist independently of insulin administration. As suggested by Harris[5] these individuals may be in a state of hyperinsulinism, induced perhaps by habitual carbohydrate feeding. Hypoglycemia has been noted by Levine, Gordon and Derick[9] and by Benger and Martens[7] during prolonged exercise. Symptoms of fatigue, hunger and weakness experienced in this condition have been relieved by the ingestion of carbohydrate.[8] These symptoms are also experienced by a large group of obese individuals on low-caloric diets and are particularly aggravated by exercise.

These observations raise a number of pertinent questions, which possibly suggest a relationship between transient hypoglycemia and other factors involved in obesity. Are certain individuals potentially in the state of hypoglycemia and fail to exercise because of a natural effort to prevent or relieve their symptoms? Is the abnormal craving for carbohydrate a further effort to relieve this distress? Is the storage of fat-forming substances facilitated and the withdrawal of food energy from the tissues interfered with in obesity? Is there a disturbance which permits certain food products to be misdirected to channels from which energy is not readily derived? The present diet was devised, therefore, to throw light on the time of occurrence and relief of symptoms in obese individuals and to determine if weight could be lost when the carbohydrate portion of the daily total caloric intake was supplied during effort in a readily available form. It seemed that the administration of carbohydrate in this manner would supply energy and because of its immediate utilization would permit only a minimum storage of fat.

Preliminary Observations. A group of obese student nurses in the Jefferson Hospital was studied through the coöperation of Miss Clara Melville and Miss Nora E. Shoemaker. So far as possible the presence of endocrine dysfunction was ruled out by metabolic and galactose-tolerance tests and physical examinations.[9] Several urine examinations were also made to determine the presence of glycosuria. If this was noted, the patient was not permitted to follow the diet. This was also true if a history of recent or chronic infection was noted or if any disturbance other than one definitely related to obesity was present. As it was not feasible to determine the chemical constituents of the blood, the question of a possible hypoglycemia was considered from a symptomatic standpoint.

In the first part of the investigation the nurses selected their own diets without regard for total calories or the types of food. The diets ranged between 1800 and 3000 calories and usually contained an excess of carbohydrate. The diets were then recalculated so that fat and protein were taken at meal time and except for that contained in other foods the carbohydrate was supplied

largely between meals as dextrose candy.* The total intake of candy was between 100 and 175 gm. daily. The patients were advised to walk twelve blocks both in the morning and afternoon, and to consume the largest portion of candy during exercise. A fairly constant loss of weight occurred in six individuals during a period of three weeks. The greatest loss was 10.5 kg. There was freedom from symptoms except moderate constipation, transient dryness of the throat, increased thirst, and on days when insufficient exercise was taken, a loss of appetite and a sensation of fullness in the stomach. Five individuals failed to lose weight on this plan; in two of these there was insufficient exercise; the question of endocrine dysfunction was raised in two patients and the fifth individual was unable to follow the diet satisfactorily.

The Dextrose Moderately Restricted Dietetic Regime. In a further group of nurses the information obtained from the study of the first series was utilized. As the patients on a diet of 1800–3000 calories (including dextrose) were not troubled with weakness or hunger a lower caloric intake was instituted. On a 1200 to 1400 caloric intake consisting of fat and protein supplied at meal time and dextrose candy between meals (100 to 150 gm.) weight was lost comfortably.

The plan of diet was as follows: On the first three days, a so-called diet-symptom chart (figure) was filled out as follows: The patient tabulated in detail the amount and type of food consumed without restriction during the day. In addition the amount of exercise and the symptoms experienced during a period of seventy-two hours were recorded. On the fourth day, the patient was placed on a 1200 or 1400 caloric diet which was essentially a 3 to 5 per cent vegetable regime with 1 to 2 pieces of bread twice daily, approximately 100 gm. of meat, clear soup, one small potato, butter, milk and fruit if desired. The activities and symptoms were recorded as usual. On the fifth day, the restricted diet was continued except that, in addition, approximately 50 gm. of dextrose candy was administered at hours when symptoms of weakness and hunger were previously noted. On the sixth day, the amount of starch was further reduced but on the succeeding days sufficient

* The candy was manufactured by the Fairiston Candy Company of 1623 Chestnut Street, Philadelphia, according to a formula devised at the Chest Department of the Jefferson Hospital, which is as follows: 1000 gm. of dextrose (Corn Products Refining Company), 250 cc. of honey, 60 gm. butter and 500 cc. of water are cooked rapidly. When a temperature of 278° F. is reached the cooking is stopped. During the entire cooking the sugar is stirred vigorously. The mixture is then poured on a marble slab, flavored (peppermint, lime, raspberry, orange, vanilla and chocolate obtained from cocoa shells) and then made into taffy in the usual manner. The candy is rolled and cut into pieces weighing 4 gm. and wrapped in wax paper. Dextrose lozenges (manufactured by Llewellyn's drug store, Philadelphia) weighing 2 gm., flavored with peppermint and wintergreen, have been used with equally satisfactory results.

Name Date

	A.M.						P.M.											
Hour[1]	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Water[2]																		
Food[2]	Breakfast (approximately 200 calories)						Luncheon (approximately 500 calories)						Supper (approximately 400 calories)					
Hunger		√			√													
Weakness					√													
Fatigue																		
Drowsiness																		
Nervousness																		
Perspiration																		
Strength																		
Candy-x[3]		√			√				√	√	√							
Exercise[4]				√	√					√	√							
Weight																		

NOTES.—[1] List activities and symptoms under hour at which they occur.
[2] Give in detail amount of food and water at each meal and between meals.
[3] Record number of candies.
[4] State exercise in blocks covered.
State impression of the effect of the diet upon general condition.
Hours sleep on previous night.
Specimen of urine collected (hour).

DIET-SYMPTOM CHART.—A tabulation to show the management of the dextrose-moderately-restricted dietetic régime. Candy-x was administered at 8 and 11 A.M. when symptoms of hunger and weakness occurred. Between 3 and 4 P.M. the candy was administered in anticipation of symptoms previously noted.

dextrose up to 100 gm. was administered to relieve all symptoms. The patients were especially advised to dissolve the candies slowly in the mouth, preferably during exercise, and to take not more than one piece every thirty minutes. They were also urged to walk four blocks twice daily at the beginning of the diet and to increase this gradually until at the end of two weeks twenty blocks were covered each day. At the end of three weeks, the regime was discontinued for ten to fourteen days and a moderately restricted diet (1400 to 1800 calories) without dextrose was prescribed. The regime was then continued as previously, if a further loss of weight was desired. As the danger of a rapid decrease was appreciated a weekly loss of over 1.5 kg. was discouraged except in extremely obese individuals. No patient was permitted to lose more than 12 kg. in three months. Throughout the diet, apart from a weekly examination of the urine, a search was made for untoward signs and symptoms. If untoward effects were noted or if the regime appeared unsuitable for the patient the diet was withdrawn at once.

Observations. The diet has been used in 44 patients for varying periods of time. In 21 instances the average loss of weight has been 1.5 kg. weekly, the greatest loss occurred usually during the first week (1.5 to 2.5 kg.). In 18 patients there has been considerable fluctuation such as a loss of 2 kg. during the first week, then a maintenance or a gain of about 5 kg. during the second week and a further loss of 1 or more kg. during the third week. During the period of ten to fourteen days when dextrose administration was discontinued and the patients followed a less restricted diet, it was rare for a gain of more than 0.5 to 1 kg. to occur. Sixteen patients have been on dietetic management for three months. The greatest loss has been 12 kg.; the average being 7 kg. Seven of this group have been on a moderately restricted diet after discontinuing the dextrose regime six weeks and show a total average loss of 5.5 kg. One patient has had no gain in weight two months after having lost 6.5 kg. although she had returned to a comparatively unrestricted diet. So far as determined there have been no ill effects other than transient headaches occasionally at the beginning of the diet or when 3 to 4 pieces of candy have been eaten in close succession. In a few instances, constipation has been noted and in one patient acne occurred. No albumin, sugar or acetone have been found in the urine when the usual tests were employed. It is noteworthy that the diet has caused no mental depression and that gastric distress previously noted has been relieved in many instances. It appears that the administration of dextrose has contributed to the comfort of the patient by preventing hunger, weakness and fatigue. In not a few instances the special craving for starch which was present before the diet was instituted has either disappeared or has been considerably reduced. The failures have been due apparently

to an improper selection of patients such as possible endocrine disturbance and a personal indifference of the patient toward obesity.

Comment. The present study suggests that a rearrangement in the time of intake of certain foods by obese individuals tends to influence a loss of weight. The plan of diet is essentially one of two parts: the first part is one of moderate starvation, (approximately 1200 to 1400 calories). In this all protein and most of the fats are supplied at meal time. The second part consists of carbohydrate (dextrose) administration (100 to 400 calories). This provides a total caloric intake of 1300 to 1800 calories daily. The carbohydrate is supplied during effort or at other times specifically to overcome symptoms of fatigue, hunger, nervousness and weakness. In proposing the diet a possible transient hypoglycemia was suggested to explain the abnormal intake of carbohydrate in obesity. This was studied largely by noting the appearance and disappearance of symptoms in relation to various foods. Dextrose was found to relieve these symptoms quite consistently so that individuals could tolerate, with comfort, a moderately low-caloric diet. That the intake of large quantities of dextrose (150 to 200 gm.) apparently does not cause an increase of weight if administered according to this plan is suggested in the study of individuals in whom the customary total dietary intake was 1800 to 3000 calories. It appears that when carbohydrate is supplied during exercise it is used, to a considerable extent, as fuel. If this be true the weight loss may be explained on the basis of insufficient food for maintenance during periods of rest, the dextrose supplied during exercise being sufficient to prevent the occurrence of symptoms. Although a specific dynamic action of dextrose (or protein) as supplied at different periods during the day may be considered, it seems more likely that loss of weight occurs essentially as a result of moderate starvation. In considering the question of the sugar-regulating mechanism, the interesting work of Lennox[10] should not be overlooked. He suggests that patients may utilize carbohydrate to better advantage perhaps if it is given repeatedly in small amounts. Whether the augmented disposal facilitates glycogen formation in the liver and tissues is yet to be proved. If it be true that the glycogen reserve is restored, the increased supply of energy would tend to influence the amount of food required. Excessive consumption of starch to relieve symptoms of hypoglycemia as practised by obese individuals becomes unnecessary and, therefore, this source of fat formation is lessened.

Obviously. the present study fails to throw light upon the various mechanisms involved in obesity. The data are presented merely to suggest that some disturbance in the utilization or mobilization of sugar may be a factor in obesity. A regime as outlined may be found of value in reducing the body weight, especially in those individuals who have an abnormal craving for sugar.

Summary. 1. The total customary caloric intake (1800 to 3000 calories) was rearranged in a series of 11 obese young women so that the carbohydrate portion was administered between meals as dextrose candy.

2. In six instances, an average weekly loss of 1.5 kg. occurred. This suggested that dextrose administered under conditions of the experiment was utilized largely as fuel.

3. To a further series, a diet of between 1100 and 1400 calories, derived largely from fat and protein was administered at meal time. In addition dextrose candy (100 to 150 calories) was administered between meals usually during exercise or at times when symptoms of fatigue, hunger and weakness were experienced.

4. A fairly constant loss of weight occurred apparently without untoward effect or discomfort to the patients.

5. It appears that weight loss to a considerable extent was due to moderate starvation at meal time, the dextrose being used principally to relieve symptoms and to supply energy during effort.

6. It is suggested that a disturbance in carbohydrate metabolism may be responsible for the storage of fat and for certain hypoglycemic-like symptoms occurring perhaps because of insufficient available glycogen.

7. A plan of diet has been suggested.

We are indebted to Dr. C. W. Nissler for valued assistance in the metabolic studies and to Misses Martha Walker, Mary Hortense Lewis and Irma Reaves of the dietetic department for their valued help in the preparation of the diets, and to Miss Mary A. Cushen, supervisor of nurses at the chest department and the student nurses of the Jefferson Hospital; without their kindly coöperation this study would have been impossible.

REFERENCES.

1. Howard, C. P.: Obesity, Oxford Medicine, Oxford University Press, 1921, **4**, 195.

2. Williams, Leonard: Obesity, Oxford University Press, 1926, Chap. 4, p. 122.

3. Mason, E. H.: The Treatment of Obesity, Canadian Med. Assn. J., 1924, 14, 1052.

4. Du Bois, Eugene F.: Basal Metabolism in Health and Disease, Lea & Febiger, Philadelphia, 1927, p. 228.

5. Harris, Seale: Hyperinsulinism and Dysinsulinism, J. Am. Med. Assn., 1924, **83**, 729.

6. Levine, S. A., Gordon, Burgess, and Derick, C. L.: Some Changes in the Chemical Constituents of the Blood following a Marathon Race, J. Am. Med. Assn., 1924, **82**, 1778.

7. Benger, G. C. E., and Martens, J. C.: Blood Sugar during Exercise, Klin. Wchnschr., 1924, **3**, 1860.

8. Gordon, Burgess, Kohn, L. A., Levine, S. A., Matton, Marcel, Scriver, W. deM., and Whiting, W. B.: Sugar Content of the Blood in Runners following a Marathon Race, J. Am. Med. Assn., 1925, **85**, 508.

9. Nissler, C. W., and Gordon, Burgess: A Study of the Factors which Influence the Metabolism in Young Women (unpublished).

10. Lennox, W. G.: Stimulation of the Sugar-regulating Mechanism as shown by Duplicate Blood-sugar Curves, J. Biol. Chem., 1927, **73**, 273.

UNUSUAL TYPES OF HEMORRHAGIC DISEASE.*

By Herbert Z. Giffin, M.D.,
ROCHESTER, MINN.

One who is especially interested in the study of hemorrhagic disease can usually make a definite diagnosis of hemorrhagic purpura without much difficulty, and the differentiation of hemorrhagic purpura and acute aplastic anemia with hemorrhagic features is possible after careful observation. There are, however, many facts with respect to coagulation of the blood and hemorrhagic disease that are not as yet explained. The unusual types of hemorrhagic disease offer opportunities which, if they could be accepted by the clinical physiologist, would elicit facts that would materially augment our knowledge concerning the coagulation of the blood and the etiology of hemorrhage.

A review of the cases of hemorrhagic disease which I have observed at the Mayo Clinic in the last five years has disclosed a group of exceptional importance in this connection.

Simultaneous Development of Splenic Anemia and Hemorrhagic Purpura. Two cases were observed in which marked splenomegaly and a secondary type of anemia and leukopenia were associated, and in which the clinical laboratory features were suggestive of hemorrhagic purpura.

Case I.—A woman, aged twenty-eight years, came to the Mayo Clinic February 18, 1925. Symptoms had appeared with an attack of influenza in 1918, which was followed by pneumonia and excessive bleeding from the nose. The bleeding recurred and purpuric areas developed. In 1920, 1921, 1924 and 1925 there were hemorrhages from the stomach. The patient also complained of pain in the splenic area.

The hemoglobin was 35 per cent (Dare), erythrocytes numbered 2,900,000 and leukocytes 1600; the differential count was not abnormal. The platelets were reduced to 64,000 and 92,000; the bleeding time, however, was not prolonged. The tourniquet test was positive. The spleen was greatly enlarged but was reduced to the level of the navel by a series of radium treatments. Transfusions were given with slight improvement. Leukopenia was persistent and the reticulated cell count somewhat high, 3.5 per cent. Culture of the blood was negative. Prothrombin time was slightly prolonged and retractility of clot was delayed. Splenectomy was finally decided on and performed June 4, 1925. The spleen weighed 936 gm., and moderately severe cirrhosis of the liver was found at operation. The leukocytes rose from 1700 to 10,800, and the platelets from 60,000 to 252,000. At the time of the last report, in December, 1926, the patient was in satisfactory condition, no bleeding had occurred, and she was working regularly.

* Abridgment of paper read before the Association of American Physicians, May 2, 1927.

Comment. This case presents a combination of the features of splenic anemia and of hemorrhagic purpura, both conditions apparently appearing at the same time. The marked enlargement of the spleen, the gastrointestinal hemorrhages, and the persistent leukopenia are characteristic of splenic anemia. Epistaxis, recurrent purpura, low platelet count, and delayed retractility of clot are consistent with a diagnosis of hemorrhagic purpura. It will be noted however, that only occasionally was the bleeding time definitely prolonged.

CASE II.—A man, aged thirty-five years, came to the Mayo Clinic in September, 1924. He gave a definite history of having had malaria in childhood, which might have accounted for the initial enlargement of the spleen. Bleeding of the gums began at the age of fourteen years, nosebleed recurred several times a year, and bleeding was excessive from cuts and scratches. There was no history, however, of purpura or petechiæ or of bleeding elsewhere. The family history was negative for evidence of hemorrhagic disease.

At the time of examination the blood showed well-marked secondary anemia. The leukocytes numbered 2900; the differential count showed nothing of significance. The platelet level was low, the count varying from 66,000 to 106,000. Bleeding time was slightly prolonged and coagulation time by the Boggs method and coagulation time by the Lee and White method, and calcium time were all within normal limits. Prothrombin time was slightly prolonged. A test of the retractility of clot is not recorded. Splenectomy was performed September 16; the spleen weighed 1100 gm. and the liver was definitely cirrhotic. Two years after the operation the patient's general health was excellent and hemorrhage had not recurred.

Comment. The marked enlargement of the spleen and the secondary anemia with leukopenia were suggestive of splenic anemia; the low platelet level, the slightly prolonged bleeding time, and the long-continued history of recurrent hemorrhage are features ordinarily found with hemorrhagic purpura.

Cases of splenomegaly with mild purpura are not uncommon. The purpura is clearly a secondary manifestation. Cases such as those described herewith, in which the syndrome of splenic anemia is associated with more marked purpura and with coagulation features suggestive of hemorrhagic purpura, lead to the suspicion that the pathologic condition in the spleen may be of such a nature as to predispose to the development of hemorrhagic purpura. Inasmuch, however, as most cases of splenic anemia do not manifest hemorrhagic features, a specific influence must be present in these cases.

Severe Hemorrhagic Disease Occurring in Four Generations. CASE III.—A woman, aged thirty-three years, came to the Mayo Clinic in December, 1922. She was weak and anemic, having suffered from epistaxis since the age of one year. At times the bleeding was extreme. After puberty, menstruation became profuse. When she was twenty years of age she began having attacks of hematemesis and melena, and following this from

three to six attacks of gastrointestinal bleeding had occurred each year and she was confined to bed for a month or two at a time. There was excessive bleeding from scratches. A few petechiæ were occasionally present but purpura occurred only on bruising. The patient's mother, maternal grandmother, and maternal great grandmother had experienced frequent epistaxis and profuse menstruation, and also profuse bleeding from cuts; they had not, however, had gastrointestinal hemorrhages.

The patient was under my observation for approximately five months. Repeated platelet counts were normal or high. The coagulation time by the Boggs method was always normal; bleeding time was consistently prolonged. Coagulation time by the Lee and White method and calcium time were consistently normal. The prothrombin time was quite consistently prolonged. Retractility of clot was not estimated. The hemorrhagic disease was complicated by the presence of duodenal ulcer, which was responsible at least for the initiation of the gastrointestinal hemorrhages; the bleeding was much more severe than that which ordinarily occurs with peptic ulcer. Marked anemia was constant; at one time the hemoglobin was as low as 25 per cent (Dare).

Comment. The family history and the patient's clinical history are suggestive of hemophilia; however, the hemorrhagic disease had occurred in the women of four generations. The high platelet level and the long prothrombin time are consistent with a diagnosis of hemophilia, but the normal coagulation time by the Lee and White method is not. The possible existence of a form of familial purpura of severe grade best explains the features of the case, while the normal coagulation time and the high platelet level indicate that fundamentally the bleeding may be the result of some deficiency of the blood which has not yet been identified.

Severe Hemorrhagic Disease with all the Features of Hemorrhagic Purpura Except Thrombocytopenia. CASE IV.—A girl, aged nine years, was admitted to the Mayo Clinic, June 4, 1924. She had had epistaxis since the age of fourteen months. The bleeding had recurred at intervals of from one week to two or three months, and often when the bleeding was severe it became necessary for the mother to pack the nose. Purpuric spots were frequently present and occasionally there was bleeding from the gums. Cuts did not bleed excessively. The family history was negative for hemorrhagic disease.

The hemoglobin was 16 per cent (Dare), erythrocytes numbered 1,380,000 and leukocytes 18,000. The differential count showed only 8 per cent lymphocytes; the platelet count was 352,000. Examination of the capillaries of the nail-fold showed much irregularity of contour. The Wassermann test was negative. The patient remained under continuous observation from June 4 to September 20. The coagulation time was normal, bleeding time prolonged, and retractility of clot absent, but the platelet count was at all times within normal limits. Several badly infected teeth were extracted without serious difficulty. Bleeding from the nose, however, continued almost constantly. Nine intramuscular injections of whole blood, four transfusions with citrated blood, and three transfusions by the direct method were given; and fibrogen, calcium chlorid, epinephrin, thromboplastin, and coagulen (Ciba) were all administered at various times. Although transfusions improved the blood somewhat, no definite control

of bleeding was brought about by any of these measures, and in spite of the atypical features of the case, splenectomy was advised. The operation was performed August 23, 1924. There was a great deal of hemorrhage, and ecchymoses and petechial hemorrhages were noted within the abdomen, and more of these were also caused by handling the viscera. The spleen weighed 140 gm. and its fibrous tissue was slightly increased. Bleeding from the wound was excessive after splenectomy, and epistaxis continued. There was no change in any of the coagulation tests during the two months of postoperative observation; bleeding time was prolonged, and retractility of clot absent. Later, however, the patient's general condition gradually improved; epistaxis became much less frequent, the anemia lessened and she was able to attend school. There has been no opportunity to retest the features of coagulation recently.

Comment. This condition cannot be classified as hemophilia, hemorrhagic purpura, or aplastic anemia. Against a diagnosis of hemophilia are an absence of a family history of hemorrhagic disease, a normal coagulation time, and the absence of involvement of the joints. Against a diagnosis of hemorrhagic purpura are the persistently high platelet count, the fact that the platelet count did not rise following splenectomy, and the unusual postoperative bleeding from the wound. Against a diagnosis of aplastic anemia are the long duration of the anemia, the persistently high leukocyte count, and the high platelet level. It is obvious that some unknown factor is present which renders a satisfactory diagnosis impossible.

Severe Hemorrhagic Disease, Extremely High Viscosity of the Blood and other Changes of Uncertain Significance. CASE V.—A man, aged forty-seven years, came to the Mayo Clinic, in July, 1925. He was weak and anemic. He had been a missionary in Thibet from 1904 to 1920, during which time he lived at an altitude of 12,000 feet, and occasionally of 18,000 to 20,000 feet. He was well during this period save for occasional attacks of palpitation and tachycardia. He returned to America in 1920, when the first hemorrhage occurred after tonsillectomy. In 1921 and 1922, profuse bleeding followed extraction of teeth. In 1923, a swelling accompanied by bluish discoloration appeared in the popliteal space. In 1924, the left knee became swollen and painful. In 1925, hematuria, associated with fever of 103°, lasted eight days. There had been intermittent bleeding from the gums since 1921, and this had been continuous for the eight months preceding examination. He had had obstinate epistaxis occasionally since 1923 and had also bled from three small telangiectatic areas on the face. He had noticed discoloration of the skin following slight bruises. There was no family history of hemophilia or other hemorrhagic tendency.

The patient was under observation for a month in 1925 and for approximately three months in 1926, during which time repeated estimations were made of the factors of coagulation. The platelet level was definitely low, although an occasional normal count was obtained. The coagulation time by the Boggs method was consistently prolonged; the bleeding time was variable, from one minute to one hour. The coagulation time by the Lee and White method was not definitely prolonged, varying from six to eleven minutes. Calcium time was normal. Prothrombin time on various occasions was normal or moderately prolonged. Normal retraction of the clot occurred in three hours. The fragility of the red cells was normal; the

volume index of the red cells was 0.95. Examination of the eye grounds revealed engorged and tortuous retinal veins with scattered retinal hemorrhages. Blood counts showed the characteristics only of secondary anemia; the hemoglobin was at one time as low as 20 per cent (Dare). The spleen was not palpable. During the period the patient was observed, the bleeding occurred chiefly from the nose and gums, and was not controlled by transfusions or the various coagulants.

Comment. The most remarkable observation in this case was an extremely high viscosity of the blood; four estimations averaged 31, as compared with a normal of 4.5 (Hess viscosimeter). The whole blood volume was slightly increased; the plasma volume was definitely increased. The increase in plasma volume was best accounted for by the anemia. The percentage of red cells on hematocrit was 18 per cent and of plasma 82 per cent. Estimations of the blood urea, uric acid, sugar, chlorids, amino acids, calcium, and inorganic phosphates were all within normal limits. The serum protein, however, was found to be 11.6 per cent (normal 6 to 8 per cent), 22 per cent of which was albumin and 78 per cent globulin; this is a reversal of the normal percentage and indicates approximately a normal absolute amount of albumin. Both the plasma and the serum had a peculiar sticky consistency. Determinations of the viscosity of the plasma and of the serum were both 29. The fibrinogen was normal in amount, 400 mg. for each 100 cc. A report received in April, 1927, stated that the patient continues to bleed despite all efforts, and the erythrocytes have become reduced to 1,940,000.

There are several other interesting features in this case. The possible effect of altitude and the change of habitat from high to low altitude should be considered. It was suspected that the patient might have been polycythemic as the result of his long-continued residence in a high altitude; this, however, could not be proved. The clinical features of the case are suggestive of severe hemorrhagic purpura. Although the platelet level was consistently low, the other coagulation tests were variable. There was no definite evidence of hemophilia. (There was no indication that the condition was due to any disease endemic to the Orient.) The high viscosity of the blood cannot be adequately explained; it is strongly suggestive that the hemorrhagic condition is entirely of a secondary nature.

Summary. A group of cases of severe hemorrhagic disease presenting unusual features has been reported. Cases of splenomegaly in which mild types of purpura occur are not uncommon, but in the 2 cases reported the features of splenic anemia are associated with a more severe type of purpura which shows the coagulation features of hemorrhagic purpura. It would naturally be inferred that the purpura, even in this type, is of a secondary nature. It

might also be inferred that some specific influence of the spleen itself, probably related to destruction of platelets, leads to varying degrees of purpura; and, moreover, that hemorrhagic purpura may be only a more severe manifestation of certain types of mild purpura even though the cases of mild purpura do not show all of the characteristic features of hemorrhagic purpura on examination of the blood.

An instance in which severe hemorrhagic disease occurred in the women of four generations without the characteristics either of hemophilia or of hemorrhagic purpura suggests that the bleeding may be due to some deficiency of the blood that has not yet been identified.

An instance of severe hemorrhagic disease with all of the features of hemorrhagic purpura except thrombocytopenia also suggests the possible presence of some unknown factor of coagulation which renders diagnosis at present impossible.

A case of severe hemorrhagic disease with extremely high viscosity of the blood, due to an enormous increase in the serum globulin, and other changes of uncertain significance emphasizes the lack of knowledge concerning the proteins of the blood and presents a clinical syndrome which, so far as I know, has not been recorded.

THE IMMEDIATE EFFECT OF ARTERIAL LIGATION.

An Experimental Study.

By Herman E. Pearse, Jr., A.B., M.D.,
BALTIMORE.

(From the Department of Surgery, Johns Hopkins Medical School.)

Arterial Ligation. The effect of a ligature upon an artery has been extensively studied since the time of Petit.[15] This field has received attention from such distinguished men as Bell,[1] Hunter,[7] Virchow,[20] Billroth,[2] Kocher[10] and others. Yet the effect of arterial ligation upon the organism as a whole has received little attention. It is strange that such is the case for in the ligation of large arteries surgical accidents occur. Most prominent of these may be mentioned cardiac collapse, pulmonary irregularities, hemiplegia, convulsions and coma, events of such magnitude, that they warrant study of the effect on the circulation of occlusion of a large channel. It is the purpose of this paper to present such a study of the immediate effect of arterial ligation on the circulation.

Methods. The animals used were adult dogs, which in every case, received preliminary medication of morphia ¼ gr. and ether anesthesia. Since a fluctuating blood pressure is produced by ether administered irregularly, it was usually given by tracheal insufflation.

Arterial blood pressure was recorded with a mercury manometer. The pressure was obtained by three methods: (1) Cannulation of the main artery; (2) cannulation of a lateral branch; (3) insertion of a small needle into the artery without obstructing the flow of blood through this channel.

Venous pressure was read with a citrate manometer connected to a cannula inserted through the jugular vein into the right auricle.

Cardiac size was estimated from roentgenograms taken with the tube in a constant position and a constant distance from the target. The cardiac shadow was also observed for the duration of some experiments by using a fluroscopic screen.

The peripheral capillaries were observed by Hooker's[6] method.

Changes in Arterial Blood Pressure with Arterial Ligation. Kast,[8] Sonnenburg,[19] Halsted[5] and Makins[12] have observed, as is to be expected, that the arterial pressure falls distal to a ligature. Halsted[5] and Reid[18] have shown that in an artery, partially occluded by an aluminum band, there is a fall in systolic, a rise in diastolic, and a diminution in pulse pressure distal to the constriction. Further it has always been noted that following arterial ligation, there is a residual peripheral pressure. This residual pressure is elevated by ligation of the corresponding vein. Following the ligation of a large artery, the peripheral pressure never returns to its former level. Finally, aside from these peripheral arterial pressures, many other studies have been made on the extremities to determine the cause of gangrene following arterial ligation.

It is strange that so little attention has been directed toward the change in pressure proximal to a ligature. Mall[13] found that when the original carotid pressure was 144 mm. Hg. it rose to 240 mm. Hg. with ligation of the aorta. It then fell to 230 mm. Hg. in thirty seconds and in eighty seconds rose to 252 mm. Hg. In the experiments here reported particular attention was directed to this question, for if harm comes to the organism, as a result of arterial ligation, then the pressure proximal to the ligature will be a factor in its causation. From another point of view, these data are desirable since if the proximal pressure is elevated, it may serve to dilate forcibly collateral channels and so maintain the viability of peripheral parts.

In all of the experiments undertaken, there was a rise of arterial blood pressure proximal to the ligature. This is demonstrated by Fig. 1. This rise is greater the larger the vessel occluded. The results obtained are shown in Table I.

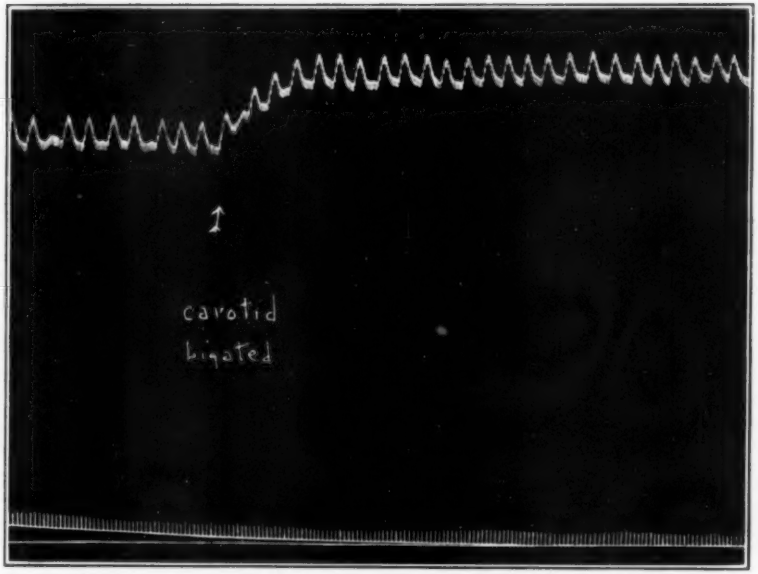


FIG. 1.—The rise of arterial blood pressure proximal to a ligature on the carotid artery.

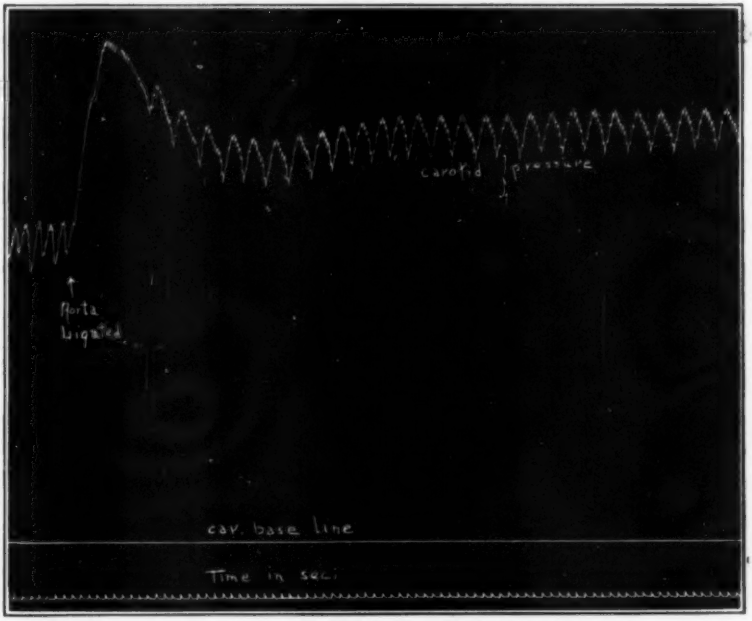


FIG. 2.—The effect on the carotid blood pressure of ligation of the aorta.

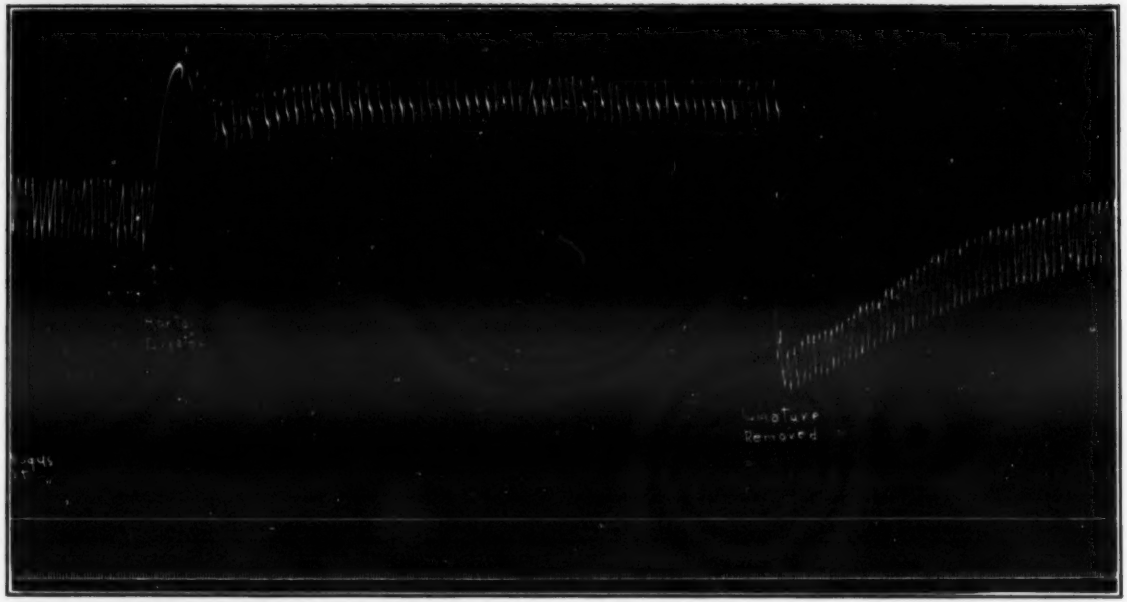


FIG. 3.—The changes in the carotid blood pressure following ligation of, and removal of the ligature from the aorta.

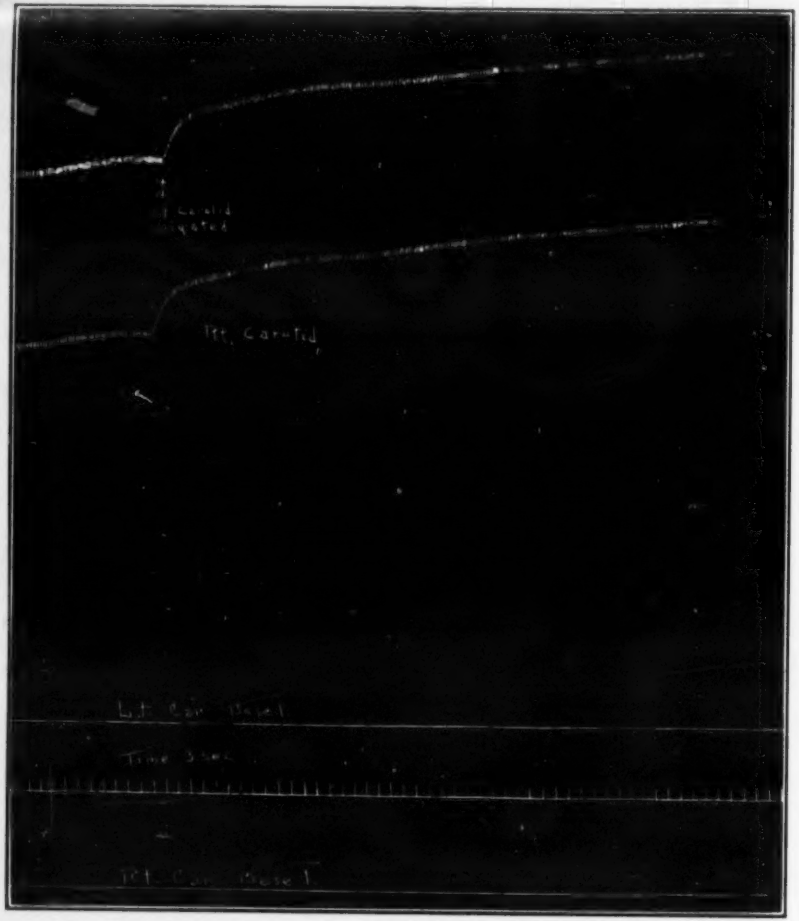


FIG. 4.—The simultaneous rise of arterial blood-pressure in both carotid arteries following the ligation of one of these vessels.

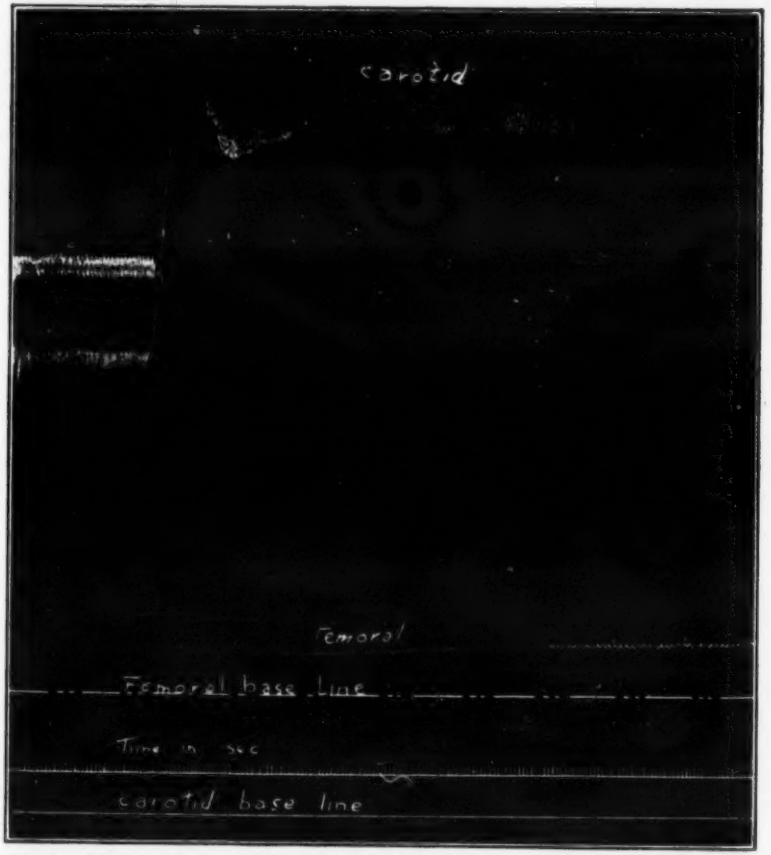


FIG. 5.—The synchronous nature of the rise proximal, and the fall distal, to a ligature.

FIG. 6.—Before ligation.

FIG. 7.—Two hours after ligation of the aorta.

TABLE I.—THE RISE IN ARTERIAL BLOOD PRESSURE PROXIMAL TO A LIGATION.

Artery ligated.	Original pressure.	Immediate rise.	30 seconds later.	1 minute later.	5 minutes later.
1. Aorta	130	202	162	172	173
2. "	128	219	190	198	199
3. "	102	176	160	166	180
4. "	110	192	152	158	170
5. "	152	213	182	186	196
6. Carotid	146	175	178	180	175
7. "	119	134	134	138	142
8. "	168	178	182	186	190
9. "	112	120	122	118	120
10. "	169	178	180	182	182
11. Femoral	134	140	143	142	136
12. "	122	126	128	128	126
13. "	142	146	148	148	147
14. "	114	118	118	119	120
15. "	124	129	128	126	124

It will be seen from this data that, in most cases, following the immediate rise in pressure, there occurs a fall, followed by a slower, better sustained secondary rise. This is best observed in the pressure obtained following ligation of the aorta and is illustrated in Fig. 2.

It will be noticed in Fig. 2 that there is a considerable drop in the pressure following the initial rise after ligation. In some cases, this amounted to 40 mm. Hg. This is an interesting fact for it would seem to denote a very rapid compensating mechanism. If the system is allowed to become adjusted to the obstruction and the ligation is suddenly removed, there is a sudden sharp fall in pressure which quickly rises to the normal level. The shape of the curve becomes a mirror image of that caused by ligation. This data is given in Table II, and illustrated by Fig. 3.

TABLE II.—THE CHANGE IN CAROTID BLOOD PRESSURE AFTER LIGATION AND AFTER RELEASE OF OBSTRUCTION OF THE AORTA.

Original pressure	Immediate rise.	30 seconds later.	1 minute later.	5 minutes later.	Ligation removed.	1 minute later.
125	176	150	162	160	84	113
136	183	150	154	160	98	132
138	193	171	179	180	69	130
131	189	168	172	176	72	120
164	211	198	202	209	112	170

A demonstration of the mechanics of this compensatory act would be enlightening. It is conceivable that following obstruction to a portion of the circulatory bed there should be a dilatation of the parts proximal, in order to quickly compensate this increased pressure. Hence, a cardiac dilatation and an increased filling of the proximal capillaries were looked for. No immediate change in their structures was noted. It is possible that this is a vagus effect

produced by a diminution in cardiac output. Observations before and after section of the vagi were the same, and no satisfactory explanation was ever found for this phenomena.

It may be well asked, is the rise in pressure immediately proximal to a ligature reflected in other parts of the circulatory tree? This would be of special significance in relation to ligation of the carotid because of the cerebral symptoms sometimes observed following this procedure. To determine this point, the carotid or the femoral arteries of both sides were cannulated with small needles so that the pressure was obtained without obstructing the lumen. Simultaneous tracings of the blood pressure were then recorded and the artery on one side ligated. There was, invariably, an equal rise on the two sides. This is illustrated by Fig. 5.

It has been reported that the arterial pressure distal to a ligature falls to a certain residual level and then rises slowly, but never reaches its former normal position. This has been confirmed and it is noted that the distal pressure in the femoral rises more rapidly after occlusion of that artery than does its pressure after ligation of the aorta. For example, the femoral pressure fell from 176 to 15 mm. after ligation of the aorta and rose to 20 mm. in ten minutes while, in the case of ligation of the femoral artery the pressure fell from 188 to 34 mm. and rose to 90 mm. in ten minutes. The greater abundance of collateral channels probably accounts for this difference.

It is to be expected that the rise in pressure proximal and the fall distal to the ligature would be synchronous. Such is the case as is shown in Fig. 5. The simultaneous carotid and femor tracings with ligation of the aorta, shown in this figure, demonstrate the synchronous character of the proximal rise and the distal fall in arterial blood pressure after arterial ligature.

Observations on Venous Pressure. It might be expected that with ligation of a large arterial trunk, with its attendant rise in arterial blood pressure, that there would be an increase in venous pressure. This is not the case, however, for repeated attempts were made and no immediate change was found. The venous pressure was obtained by inserting a long cannula into the right auricle through the jugular vein and readings taken with ligation of the aorta at the level of the diaphragm.

Changes in the Size of the Heart with Arterial Ligation. It has been observed by surgeons that patients with cardiac disease are poor risks for operative procedures on large bloodvessels. This is especially true if the procedure necessitates occlusion of the aorta. Keen[9] has emphatically warned against this operation in the presence of cardiac weakness. That this is justifiable is shown by the subsequent data.

In normal, healthy dogs, occlusion of the carotid or femoral arteries causes no change in the size of the heart. It has been

mentioned that there was no immediate change in cardiac size following ligation of the aorta. There is, however, a gradual, progressive, cardiac dilatation which is demonstrable at the end of ten minutes after ligation. The amount of dilatation depends upon the site of the ligature. When it is placed below the renal arteries, the dilatation is rarely more than 0.5 cm., while if placed above the diaphragm, the dilatation is often in excess of 1.5 cm. (transverse diameter). This result is illustrated in Figs. 6 and 7.

It may be well to say a word concerning the sequence of events leading up to the death of an animal, following ligation of the thoracic aorta. This procedure is not tolerated by dogs. It has been noted that there is a rise in arterial blood pressure proximal to the ligature. This elevated pressure persists and there follows a progressive cardiac dilatation. The peripheral capillaries became congested. There being no outlet for the blood, it is dammed back in the pulmonary circuit. The lungs become engorged and pulmonary edema results. The animal exhibits signs of air hunger and dies a death of suffocation. Thus, the increased arterial pressure proximal to the ligature results in a chain of events that lead to the death of the animal.

Discussion. It is to be expected that a greater effect will be produced upon the circulation by ligation of the aorta than of any other large artery. In fact, prior to a century ago, it was considered to be instantly fatal to occlude this structure. The operation was first done in man by Sir Astley Cooper[3] in 1817. Following this experience, experimental work was done by Pirogoff,[16] Monteiro,[14] Porta,[17] Sonnenburg,[19] Kast[8] and Kümmel[11] who showed that ligation of the aorta was a feasible procedure and that the collateral circulation developed sufficiently to assure viability of the peripheral parts. But it has been recognized that the occlusion of this great vessel puts a strain upon the circulation. The warning has frequently been given that it is dangerous to carry out this procedure in the presence of myocardial weakness or other arterial disease. But since the usual indication for ligation of the great vessels is for the cure of aneurysm and since the presence of aneurysm usually presupposes an extensive arterial disease, then it is obvious that the presence of a normal circulation is an ideal seldom realized, so that the increase of pressure following arterial ligation is placed upon a system already weakened by disease. That this increased pressure is the primary cause of some of the surgical accidents occurring immediately after occlusion of the great vessels, would appear probable. The cardiac and respiratory irregularities have been demonstrated in the data given. There is less certainty about the cause of the cerebral accidents since they do not occur in experimental animals. In the past, they have been ascribed to cerebral anemia, the embolism and "arterial stupor of Veau" have been suggested. Cutler[4] has given proof of the sensitivity of the brain

to an inadequate circulation. Yet, with the free anastomosis of the vertebral and carotid vessels in the circle of Willis, and with a knowledge of how quickly the circulation returns to a peripheral part, lacking such an anastomosis, it is difficult to conceive of anemia in this location.

It has never been suggested that these cerebral symptoms might be due to an increased arterial pressure in the cerebral vessels. It has been shown that with ligation of the carotid on one side there is an elevation of pressure in the opposite artery. Further, clinical evidence shows that these lesions often come suddenly after the vessel is ligated and are most apt to occur in a subject past middle age. Finally, the cerebral vessels, especially in the presence of arterial disease, are susceptible to rupture with resultant neurologic lesions. Is it not significant that aneurysm, for which the carotid is most often ligated, and hemiplegia are manifestations of the same vascular disease?

There is another phase to the problem which has not been considered: namely, that the increased proximal pressure may be an aid in the development of collateral circulation to the peripheral parts. Recently, Dr. Lewis has advocated ligation of the femoral artery below its profunda branch for the relief of thromboangiitis obliterans of the lower extremities. This has proven beneficial and is most logical since the main arterial channel being diseased, the blood is shunted to the extremity through the vessels of the crucial anastomosis which have not been involved in the disease process. If the arterial blood pressure is elevated proximal to a ligature, in man, then this increased pressure may well serve to dilate the collateral channels and so increase the circulation to the extremity.

Conclusions. 1. Ligation of a large artery results in an increase in arterial blood pressure proximal and a decrease distal to the ligature. Cardiac dilatation and pulmonary edema follow sudden occlusion of the aorta.

2. To avoid a sudden increase in arterial pressure, the occlusion of the great vessels should be a gradual process.

3. The elevated proximal pressure may well be a factor in dilating the collateral channels and securing viability of the peripheral parts.

BIBLIOGRAPHY.

1. Bell, John: Principles of Surgery, London, 1815, **1**, 141.

2. Billroth, Theodor: Die allgemeine chirurgische Pathologie und Therapie, Berlin, 1863.

3. Cooper, Sir Astley: Cooper and Traver's Surgical Essays, 1817, **1**, 83.

4. Cutler, E. C., Levine, S. A., and Beck, C. S.: The Surgical Treatment of Mitral Stenosis; Experimental and Clinical Studies, Arch. Surg., 1924, **9**, 689.

5. Halsted, W. S.: Partial, Progressive and Complete Occlusion of the Aorta and Other Large Arteries in the Dog by Means of the Metal Band, J. Exp. Med., 1909, **11**, 373. An Experimental Study of Circumscribed Dilation of an Artery Immediately Distal to a Partially Occluding Band, and its Bearing on the Dilation

of the Subclavian Artery Observed in Certain Cases of Cervical Rib, J. Exp. Med., 1916, **24**, 271.

6. Hooker, D. R.: The Functional Activity of the Capillaries and Venules, Am. J. Physiol., 1920, **54**, 30.

7. Hunter, John: A Treatise on the Blood, Inflammation and Gunshot Wounds, London, 1794.

8. Kast, A.: Die Unterbindung der Bauchaorta, Deutsch. Ztschr. f. Chir., 1880, **12**, 405.

9. Keen, W. W.: A Case of Ligature of the Abdominal Aorta Just Below the Diaphragm, the Patient Surviving for Forty-eight Days; with a Proposed Instrument for the Treatment of Aneurysms of the Abdominal Aorta by Temporary Compression, Am. J. Med. Sci., 1900, **120**, 251.

10. Kocher, Theodor: Ueber die feineren Vorgänge bei den Blutstillungen durch Acupressur, Ligatur und Torsion, Arch. f. klin. Chir., 1869, **11**, 660.

11. Kümmel, H.: Die Unterbindung der Arteria iliaca cummunis, Arch. f. Chir., 1884, **30**, 67.

12. Makins, Sir George: Gunshot Injuries to the Bloodvessels, New York, Wm. Wood & Co., 1919.

13. Mall, F. P.: The Contraction of the Vena Porta and its Influence upon the Circulation, Johns Hopkins Hosp. Rep., 1896, **1**, 111.

14. Monteiro, C. B.: The Abdominal Aorta Tied, Lancet, 1842, i, 334.

15. Petit, Jean Louis: Dissertation sur la maniere d'arreter le sang dans les Hemmorhagies, Mem. de l'acad. royale des Sci., Paris, 1731.

16. Pirogoff: Annalen der chir. Abtheilung des Klinikum zu Dorpat, 1839, vol. **2**.

17. Porta, Luigi: Della Alterazione Pathologiche delle Arterie per la Ligatura e la torsione, Milano, 1845.

18. Reid, M. R.: Partial Occlusion of the Aorta with the Metallic Band. Observations on Blood-pressures and Changes in the Arterial Wall. J. Exp. Med., 1916, **24**, 287.

19. Sonnenburg, E.: Einige Bemerkungen, betreffend der Herstellung des Collateralen Kreislaufes Nach Unterbindungen der Arterien in der Continuität, Centralbl. f. Chir., 1876, **3**, 689.

20. Virchow: Ueber den Faserstaff, Ges. Abhandl., 1845.

FIVE YEARS' EXPERIENCE IN THE TREATMENT OF CHRONIC AURICULAR FIBRILLATION WITH QUINIDIN SULPHATE.* †

By E. P. Maynard, Jr., M.D.,

Brooklyn, N. Y.

Before the addition of quinidin sulphate to the treatment of heart disease, auricular fibrillation was recognized as a permanent change in the mechanism of the heart beat which was to persist, except in the rather rare instances of paroxysmal fibillation, as long as the patient lived. Under ordinary circumstances, the ventricular rate could be controlled more or less successfully with digitalis, but the tumultuous beating of the heart with its distressing subjective sensations was readily induced by exertion. The patients were continually reminded of their disability and their exercise tolerance was thereby reduced. It has been suggested that the

* Read before the members of the Heart Section of the New York Tuberculosis and Health Association, May 24, 1927.

† Grateful acknowledgement is made to Dr. W. H. Lohman for permission to include many of the cases treated on his service and also for his interest and helpful criticism in the compilation of this paper.

restoration of normal sinus rhythm by the use of quinidin sulphate, by abolishing the irregular heart action and putting the normal pacemaker in control, would relieve the patients of the distress incident to the irregularity of fibrillation. The evidence so far accumulated shows clearly that auricular fibrillation can be abolished by quinidin in at least 50 per cent of cases and while the normal mechanism prevails, the patients undoubtedly are relieved of the discomfort incident to irregular ventricular action and their exercise tolerance is thereby increased.

However, in order to evaluate any new therapeutic procedure, it is necessary to determine whether its effect will be lasting enough to counterbalance whatever discomfort or danger there may be in its use. For that reason, it seemed worth while to study a series of cases of chronic auricular fibrillation treated with quinidin sulphate and followed for a period of from one to five years. This series is made up of cases from the Brooklyn Hospital Cardiac Clinic, the medical wards and a few private patients.

The method of administration of the drug was as follows: Two test doses of 0.2 gm. each were given the first day to eliminate the possibility of hypersensitivity to quinidin and if no symptoms appeared, the next day the dose was increased to 0.4 gm. every two hours for five doses. In a few patients, who failed to respond to treatment, the dosage was cautiously increased to 0.6 or 0.7 gm. every two hours and in some instances sinus rhythm was established by the larger doses where the smaller ones had failed. Later in our study, following the suggestion of Riecker,[1] the quinidin was given 0.4 gm. every four hours day and night in order to produce an even pharmacologic action throughout the course of treatment, but because of so many variable factors involved, no definite conclusions could be reached as to which was the better plan.

A total of 53 cases of auricular fibrillation has been treated with quinidin sulphate and sinus rhythm has been established in 38, or 71.7 per cent. However, in order to determine the value to the patient of this procedure, it is necessary to know how long sinus rhythm persisted. It seemed to us that sinus rhythm for a period of one month was the shortest time that could be considered of real value to the patient and this period was taken as the minimum standard of successful treatment. When analyzed from this standpoint, it appears that there were 25 cases, or 47.1 per cent, who have remained regular one month or more. There can be little doubt that six months of sinus rhythm are of benefit to the patient. Fifteen, or 28.2 per cent of the series, have remained regular for six months or more. Of these, one has been regular for thirteen months. two for fourteen months, one each for fifteen, sixteen and seventeen months, one for twenty, one for two years, two for three years and one for five years. When these patients were asked their opinion of quinidin treatment, their approval was emphatic.

Of course, it is obvious that quinidin sulphate has no beneficial action upon the course of the heart disease except such as must come from the restoration of control of the rate by the pacemaker. Therefore, it is of considerable interest to study the expected tendency to relapse to fibrillation and as this series extends over a period of five years, some data have accumulated. Out of 35 cases that have been followed to date 25, or 71.4 per cent, have relapsed to fibrillation permanently and cannot now be restored to sinus rhythm. Six, or 17.1 per cent remain regular and are active and 4, or 11.4 per cent, have remained regular until death. It has been our experience that sinus rhythm may be reëstablished five, six or seven times in the same individual but the time finally comes when further attempts are unsuccessful. However, it does not follow that because the first period of sinus rhythm was brief, the second will be shorter. The best result may be obtained in the second or third course, but except in unusual cases, fibrillation finally becomes permanent. Such an outcome is to be expected when one remembers that the morbid process continues even though the rhythm has been restored.

In evaluating a therapeutic procedure, one must take into consideration the untoward results or accidents that may follow, analogous to the operative risks in surgery. In quinidin therapy these are of two types—First, a group of annoying toxic symptoms that have no permanent effect. These consisted in this series of such symptoms as nausea, headache, dizziness, tinnitus, palpitation and diarrhea, ranging in frequency as in the order named and of no great moment. A troublesome urticaria also occurred once.

In the second group belong those accidents that are of great importance. There were 2 cases in which great respiratory embarrassment with cyanosis appeared probably at the moment when sinus rhythm was established. This condition cleared up promptly. In 2 patients a transitory hemiplegia appeared forty-eight hours after sinus rhythm, clearly of embolic origin and in each case the paralysis cleared up promptly and completely.

There was one case of collapse and sudden death which is worthy of more detailed description. The patient was a middle-aged, obese woman with auricular fibrillation of unknown etiology. When first seen, she was moderately decompensated with basal râles and swollen liver. After rest in bed and digitalis, all signs of failure disappeared and quinidin was given in the usual manner. There were no toxic symptoms from the test doses and sinus rhythm was established after 5.4 gm. of the drug had been given. At the moment of resumption of sinus rhythm she was observed by a nurse. There was considerable respiratory difficulty and the pulse was imperceptible at the wrist. The patient recovered from this attack promptly, quinidin was discontinued and she remained comfortable all day. The heart was regular. Sixteen hours later she suddenly sat up in bed,

had respiratory difficulty, became unconscious and died, the heart continuing to beat for some time after the loss of consciousness. Autopsy permission was refused. Apparently, death was due to embolism, either cerebral or pulmonary. Because the death occurred seventeen hours after the last dose of quinidin, it could not have been due to direct toxic action of the drug but rather to the altered cardiac mechanism which probably dislodged an auricular thrombus. Such tragedies are not rare and although they occur with as great frequency in auricular fibrillation and other types of heart failure not treated with quinidin; nevertheless, their occurrence after quinidin therapy seems more than a coincidence. It seems only fair that before patients are to be treated with quinidin some relative should be acquainted, as is done in surgery, with the dangers as well as the benefits of the procedure.

Toxic rhythms of various sorts were common during the course of quinidin therapy in this series and were often interesting in that they threw light on the pharmacology of the drug. Premature ventricular beats were very common and in 5 patients occurred in pairs or short runs. In another case, they were continuous, constituting an attack of ventricular paroxysmal tachycardia. Of course, this complication is dangerous being the forerunner of ventricular fibrillation and calls for discontinuance of the drug. The other common toxic rhythm was pure auricular flutter and represents a slowing of the circus movement to the point where the ventricle can pick up the rhythm at a 2 to 1 ratio. Other interesting toxic changes occurred such as 2 cases of transitory left bundle branch block and one bigeminal rhythm.

Because of the risk in quinidin therapy and the high percentage of failures, it is necessary to search for any facts that may help in the selection of cases. As has been pointed out by others,[2] the degree of decompensation is the most important single factor. In our series, sinus rhythm was established in 90 per cent of the cases in which their compensation was classified as good, 56 per cent in those that were called fair and 43 per cent in those called poor.

However, it is interesting to note that among the markedly decompensated cases, one remained regular thirteen months, another fourteen months and a third one year and eight months.

Hart[3] has suggested that the rate of circus movement might have some bearing on the chances of success with quinidin, the slow types being more favorable. In our series, no such relation could be made out, although it is only fair to state that no special methods for measuring the exact rate of the circus movement were employed. The auricular activity was simply classified as slow, rapid or variable.

Furthermore, there was no relation between the duration of the heart disease and the result of treatment. However, there did seem to be a relation between the duration of fibrillation and successful

treatment. Those cases whose fibrillation was known to have been established for a year or less, did by far the best, $66\frac{2}{3}$ per cent being successful, that is, remained regular for a month or more.

The amount of quinidin sulphate necessary to establish sinus rhythm was very variable, ranging from 0.4 gm. in 2 cases up to 46.85 gm. in one. Success was usually attained, if at all, before a total of 10 gm. had been reached but if there were no contraindications, it was often worth while to continue the drug up to 20 or even 30 gm. An individual patient often varied considerably in the amount required to establish sinus rhythm in different admissions and no general rule could be deduced.

An effort was made to make daily electrocardiographic tracings during the administration of quinidin in each case in the hope that the change from fibrillation to sinus rhythm might be photographed. We were not successful in this, but the material obtained made it possible to analyze the effect of quinidin sulphate upon the various components of the electrocardiogram. The most important effect is upon auricular activity. As has been pointed out before, the auricular waves became slower and slower until at times they made an even undulation that could be measured accurately and which was nearly, if not quite regular. At the same time the ventricle became more rapid, perhaps because it was stimulated more often by these coarser auricular waves, until at times the 2 to 1 ratio of auricular flutter existed.

After sinus rhythm had been established the *P* waves were usually of abnormal form, they were large and irregularly notched and sometimes varied in shape for several days until sinus rhythm had been firmly established. A slight irregularity in the rhythm of impulse production was occasionally observed. *A–V* conduction time was quite regularly prolonged above 0.2 seconds. In one instance it was as long as 0.34 seconds. No prophecy as to the permanence of sinus rhythm could be based upon the length of *A–V* conduction however.

Quinidin sulphate in this series had very little effect upon intraventricular conduction as measured by the *Q–R–S.* interval. This measurement either remained the same or was slightly increased.

No constant effect could be noted upon the *S–T* interval either as to its duration or direction of electrical potential. However, the *T* waves themselves tended to become taller after sinus rhythm had been established by quinidin.

To return once more to the general subject of quinidin therapy, the important question to decide is whether the benefits to be derived by the patient outweigh the trouble and danger encountered in its use. In the series of cases here presented 28.2 per cent of all patients treated, obtained six months or more of continuous sinus rhythm. Two patients have remained regular for three years and

one for five and these patients are still regular. In this series, many patients were treated, especially early in the study, who had only partially recovered from severe cardiac failure.

If quinidin sulphate is to remain in the list of therapeutic agents for the treatment of chronic auricular fibrillation, a careful selection of cases for treatment must be practised. From a study of this series and from the reports of others, the two definite criteria for this purpose are, first, relatively short duration of the fibrillation, and second, a well-compensated heart without the signs of congestive heart failure.

Summary. 1. In a series of 53 cases of chronic auricular fibrillation treated with quinidin sulphate, 38 (71.7 per cent) returned to sinus rhythm. Of these 25 (47.1 per cent) of the entire series remained regular for one month or more and 15 (28.2 per cent) kept their sinus rhythm for at least six months.

2. Evidence has been presented to show that there is a definite tendency for auricular fibrillation to become permanent. Sinus rhythm may be established five, six or even seven times over a period of years, but the time finally comes in the majority of cases when further attempts are unsuccessful.

3. One case of collapse and sudden death following quinidin therapy has been reported.

4. Various toxic rhythms induced by quinidin have been described including auricular flutter and ventricular paroxysmal tachycardia.

5. Sinus rhythm was established in 90 per cent of the cases whose degree of compensation was classed as good.

6. Short duration of fibrillation was a good prognostic sign.

7. The effect of quinidin upon the various components of the electrocardiogram had been described.

REFERENCES.

1. Riecker, H. H.: Am. J. Med. Sci., 1925, **170**, 205.
2. Viko, F. E., Marvin, H. M., and White, P. D.: Arch. Int. Med., 1923, **31**, 345.
3. Hart, T. S.: Arch. Int. Med., 1922, **30**, 593.
4. Lewis, T.: Am. J. Med. Sci., 1922, **163**, 781.

BALL THROMBUS IN LEFT AURICLE.

A Case Report.

By George W. Covey, M.D., R. Crook, M.D.,

and

Floyd L. Rogers, M.D.,

Lincoln, Neb.

The literature bearing on thrombosis of the heart with particular reference to ball thrombi has been carefully sifted by Abramson[1] and Potter[2] up to 1926. They have collected 21 cases of ball thrombus

and reported 2 new ones, making a total of 23. I have not been able to find reports of any others since Potter's article appeared.

Both authors accept the following definition of ball thrombus, quoted from Welch;[3] "(*a*) entire absence of attachment and consequent mobility; (*b*) imprisonment in consequence of excess in the diameter of the thrombus over that of the first narrowing in the circulatory passage ahead of it; (*c*) such consistence and shape that the thrombus must not of necessity, lodge as an embolus in this passage."

We wish to present the report of another case that clearly falls within this definition, as follows:

Case Report. *Clinical History and Findings.* Mrs. J. A. B., a married white woman, aged fifty-five years, had been breathless on exertion for four or five years. This symptom had been gradually increasing in severity but was always improved by a period of rest in bed. For six months, she had had evening edema of feet and legs, disappearing during the night. About May 1, 1927 a thrombotic hemorrhoid was opened by Dr. Crook, and the clots turned out. She was in bed much of the time after this because of dyspnea and edema; about May 15 she began to vomit and complain of severe pain across the upper abdomen with tenderness in the gall bladder region and along the rib margin toward the right. At this time, Dr. Crook noted rather marked cyanosis of the face, enlargement of the heart to the left, a systolic murmur over the apex, a large tender liver and edema of the feet and legs.

From that time until May 23, she remained in bed taking 15 drops of tincture of digitalis three times a day. Her heart rate had slowed somewhat but was quite irregular in rhythm.

She had not vomited for several days until the evening of May 22. There had been no chills or fever. The output of urine had been satisfactory. On May 23, Dr. Covey, saw her in consultation with Dr. Crook. She related the following complaints: Pain in the right upper portion of abdomen with tenderness, nausea, vomiting and dyspnea.

Her past and personal history revealed nothing significant except an abdominal operation years ago, supposedly because of an ectopic gestation. No rheumatic history was obtained.

Physical examination revealed a well-nourished elderly woman lying in bed, with an expression of pain and anxiety. The temperature was normal, the pulse rapid, about 110 at the wrist, absolutely irregular and with a fairly marked deficit. The blood pressure, about 166 systolic and 90 diastolic. Fairly marked cyanosis was noticeable, particularly in the face, hands and feet. There was a moderate degree of edema over the shins. The heart was enlarged well beyond the midclavicular line at the left, the apex thrust being fairly well localized and in the fifth interspace or under the sixth rib. There seemed to be some enlargement to the right of the sternum but the percussion outline was somewhat uncertain. No murmurs were heard. The rhythm was that of auricular fibrillation. The liver edge was palpable on deep inhalation. Four finger breadths below the rib margin in the midclavicular line, it was smooth and tender.

A diagnosis was made of auricular fibrillation with cardiac failure, presumably due to mitral stenosis, and we agreed to push the digitalis to the point of complete digitalization.

The patient improved, the pulse become slower and much less irregular and most of her subjective symptoms were relieved, though she still remained

in bed. Suddenly on June 18, at 9 P.M. she was seized with pain in the right leg. She was seen at this time by Dr. Rogers. The following are the notes he made during the next two days.

June 18, 1927. Patient first seen on the night of June 18, 1927. Was seen only during the absence of her physician, Dr. Crook.

9.00 P.M. Patient states that about an hour ago she had some pain in the right leg. This pain was not prolonged nor was it very severe. A short time later she had a sudden and very severe pain in the left leg. The entire part of the leg, below the knee being painful. She had been feeling somewhat better during the few days prior to the attack.

She was evidently in most severe pain. The face was flushed and of a deep red color; there was also a slight cyanotic color to the lips and finger tips.

Temperature, 98.4° F.; pulse irregular in its irregularity, 74 at wrist, 130 (?) at apex; blood pressure, 140 systolic, 90 diastolic (?). The heart was enlarged both to the left and right. There was a definite thrill and a murmur.

There were numerous petechial spots on the arms and an ecchymosis on the right hand about 1½ cm. in diameter. The right leg appeared normal. The left, below the knee, was of a slightly bluish color when first seen but within an hour was of a distinct blue color, and was then colder than the right. It was very tender. Morphin sulphate was given and repeated to control the pain.

June 19, 1927, 11 A.M. The leg is now of a more distinct bluish color, is colder and more tender. Pain is being controlled with morphin. Cyanosis about the lips and finger tips is more pronounced. The heart findings are unchanged except that the murmur and thrill are more marked.

4.00 P.M. Cyanosis more marked. The thrill is now most pronounced, and the murmur is very loud, being audible at a distance of a few feet from the patient. It is the loudest heart sound I have ever heard, and the most marked thrill I have ever felt. The murmur is presystolic in time.

9.00 P.M. Cyanosis more marked, patient unconscious, pulse weak and irregular. Leg is more blue. Heart unchanged as regards thrill and murmur. Pulse is now slower and the murmur is presystolic (?).

On the basis of auricular fibrillation, with probable mitral stenosis, arterial embolus in the leg, the development of the peculiar noisy murmur and the thrill we concluded that thrombosis, probably of the ball thrombus type, existed in the left auricle. On June 21, three days after the embolism of the leg occurred, the patient died.

Autopsy. The following are the notes made at the postmortem examination of her body.

External appearance: The body has been embalmed. It is that of a short fat woman. The left leg, from a point just above the knee downward is of a distinct red color, and larger than the right. There is a sharp irregular line of demarcation between the red edematous (?) portion and the normal thigh above. There is an old operative scar midline of abdomen below umbilicus. Primary incision reveals a very thick panniculus of fat beneath the skin. The peritoneum is smooth and there are no adhesions, increase in fluid, or enlargement of lymphatic glands, mesenteric or retroperitoneal. The appendix is long and slender and lies behind the cecum, tip pointing upward. The diaphragm reaches the fifth interspace on the right and the fifth rib on the left.

Pleural cavities: The left, is dry and contains no adhesions or other apparent pathologic lesions. The right, is dry and similar to the left.

Pericardial cavity: Has been entered by a trochar but shows no evident lesions.

Lungs: Both lungs are of normal appearance except for undue congestion, which is not so evident as it probably would have been prior to embalming.

Heart: The heart is large, weighing, when emptied of its contents 500 gm. The greatest apparent enlargement is of the right side. The auricle is markedly dilated, the wall thinned and very fibrous, particularly in the region adjacent to the entrance of the great veins, where it cuts like pure fibrous tissue.

The tricuspid valve admits the tips of three fingers and its leaflets are normal. The right ventricular wall is very thick, equalling that of the left. Its cavity is also increased in size. The pulmonary valve is normal. The root of the pulmonary artery shows a number of yellowish raised plaques, 3 to 5 mm. in diameter, about 2½ cm. above the valve. The left auricle is slightly dilated. It contains a small amount of cruor. On the outer wall, is a small mural thrombus, antemortem. The appendage is filled with antemortem clot and a certain amount of postmortem clot. Lying in the funnel-shaped approach to the mitral valve is a ball thrombus, measuring 3 cm. in diameter and weighing 16 gm. It is almost a perfect sphere and the surface is just slightly roughened, reminding one of an old golf ball whose original markings have almost been worn off. On one side, however, there is a small oval deficiency about 6 mm. long and 3 mm. wide by 1 mm. deep. Parallel with this are two wavy indentations gradually fading into the normal smooth surface beyond. Observation shows that these "waves" in the surface exactly coincide with irregularities in the mitral valve leaflets against which the ball lay and when placed in this position the "defect" noted comes precisely over the opening of the mitral valve. This ball is firm but has about the feel of a piece of sponge rubber of similar size and shape.

The mitral leaflets are adherent along their edges, reducing the opening to a curved slit, through which the tip of the fifth finger can be inserted enough that, by using a little force, it can be seen from below. There is no calcification. On the outer half of the upper surface of the anterior leaflet, there is marked warty roughening, but no fresh vegetations. The cavity of the left ventricle is small and the wall is not thickened. The aortic valve appears normal as does the root of the aorta.

Gastrointestinal tract: The stomach and intestine show no gross lesions.

Liver: Only slightly larger than normal. Capsule not thickened. Cut surface has the appearance of chronic passive congestion, not so marked as that commonly known as nutmeg liver. Gall bladder normal.

Spleen: The spleen is slightly enlarged but not otherwise abnormal.

Kidneys: The left, is of about normal size, showing a number of irregular scarlike depressions. The cortex is thinner than normal, irregular in thickness and shows considerable increase in connective tissue. The capsule strips with fair ease and leaves an evenly granular surface. The right, is similar to the left. In both, scar tissue runs from the depressed areas through to the pelvis.

FIG. 1

Suprarenals: Not examined.

Pelvic viscera: Normal except for some adhesions about the right tube. Both ovaries small, hard and fibrous.

Abdominal aorta: No remarkable abnormalities.

Head and neck: Not examined; not permitted.

Special regions: Not permitted.

Anatomical lesions: Mitral stenosis, ball thrombus left auricle; mural thrombi left auricle; dilatation right auricle with marked fibrosis of wall; dilatation and hypertrophy right ventricle; some intimal changes in pulmonary artery; chronic passive congestion lungs, liver, spleen; chronic nephritis with early contraction; old healed infarcts of kidney; probable arterial embolus in left leg about level of lower third of thigh, with death of leg.

Probable cause of death: Mitral obstruction and arterial emboli.

The accompanying illustrations show (Fig. 1) a view of the interior of the left auricle. Note the small aperture of the mitral valve

FIG. 2

FIG. 3

and the warty vegetations on the anterior leaf; (Fig. 2) the same view but with the ball thrombus lying in its position over the mitral opening; (Fig. 3) the ball thrombus by itself.

So far as we were able to determine, there was nothing in the clinical picture presented in this case prior to the abrupt occurrence of arterial embolism in the leg, that would lead the clinician to suspect thrombosis either mural or ball thrombus type. However, as is shown in Abramson's review of cases, the combination of mitral stenosis with embolism in the legs should always arouse the suspicion of cardiac thrombosis, and in this case there were the added features of the abrupt simultaneous development of the noisy murmur and marked thrill described above.

Summary. An additional typical case presenting the sign of mitral stenosis, auricular fibrillation, cardiac failure, embolism in artery of leg, loud cardiac murmur ("noise"), pronounced thrill and death is presented. The postmortem shows the presence of a typical ball thrombus occupying the left auricle, in the presence of most marked mitral stenosis.

Photographs showing the interior of the auricle with and without the ball in place and of the ball itself, are presented.

BIBLIOGRAPHY.

1. Abramson, J. L.: Ann. Clin. Med., 1924, **3**, 327.
2. Potter, Eugene B.: Ann. Clin. Med., 1926, **4**, 736.
3. Welch, Wm. H.: Allbutt's System of Medicine, 1899, **6**, 185.

BRUCELLA MELITENSIS (ABORTUS) BACTEREMIA ASSOCIATED WITH ENDOCARDITIS.

By R. W. Scott, M.D.,

AND

O. Saphir, M.D.,

CLEVELAND.

(From the Departments of Pathology and Medicine, Cleveland City Hospital and Western Reserve Medical School.)

The recent interest in the study of Brucella melitensis, stimulated particularly by Evans, justifies a report of the following case, especially as there are few references to endocarditis associated with Brucella melitensis infection. Huges reports 4 cases and Lagriffoul, Arnal and Sardon, as quoted by Sacquépée, describe 1 case of endocarditis caused by Micrococcus melitensis.

Case Report. Clinical Findings. A white male, J. S., aged twenty-one years, occupied as a laborer, first came under observation at the Cleveland City Hospital in January, 1926, complaining of fever, chills and pain over the heart, of three weeks' duration. The patient was born and reared on a farm in Hungary and with the exception of six months, which he spent in Budapest when he was about sixteen years of age, he always lived in the

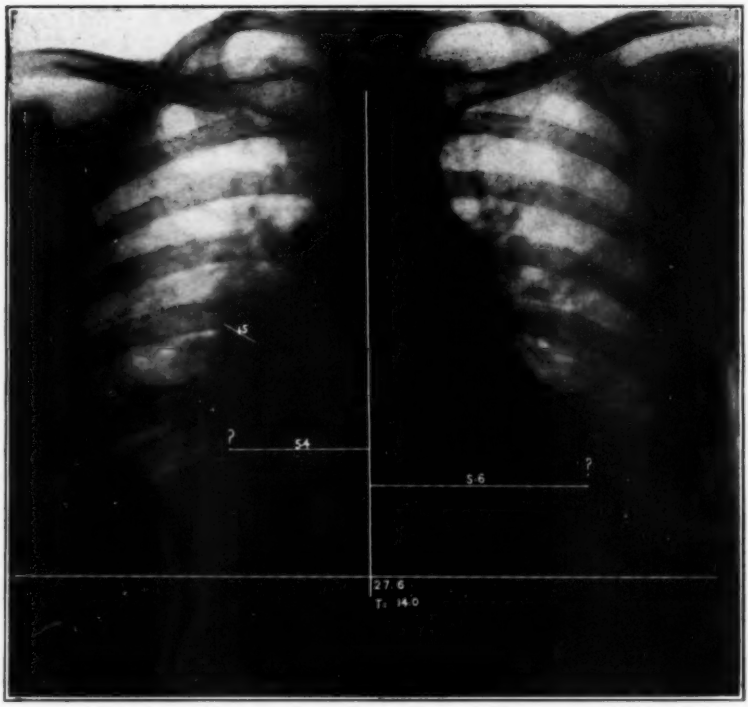


FIG. 1.—A 7-foot Roentgen ray of the heart, taken one month before death.

FIG. 2.—Photograph of the heart, showing the left auricle, with a large thrombus at the mitral orifice.

country until he came to America in 1922. At the age of thirteen he had acute rheumatic fever and was confined to bed for two weeks. A second attack occurred at the age of nineteen. Prior to the onset of his present illness, he had no cardiac symptoms. In December, 1925, he became ill with fever, occasional chills and pain over the precordium, and after treatment at home for three weeks he was advised to come into the hospital. He remained under observation for eighteen days and during this time he had a daily elevation in temperature varying between 38° and 39° C., but no chills. He was a fairly well-developed and nourished young man with no anemia, the red blood cells being 5,000,000 per c.mm. The blood Wassermann test was negative. The heart was slightly enlarged, as shown by the 7-foot plate reproduced in Fig. 1; there were clear signs of mitral stenosis, and a faint diastolic murmur was heard over the aortic area, suggesting aortic insufficiency, but the pulse was not of the Corrigan type. The cardiac mechanism was normal, rate around 100 per minute, and the electrocardiogram showed nothing unusual. The blood pressure was 118 mm. systolic; 70 diastolic. The lungs were clear and there were no signs of congestive failure. The spleen was enlarged to percussion but not palpable. Several blood cultures were negative. The patient left the hospital against advice and was not seen again until his second admission one week later, when he returned with the same symptoms as on the previous admission. His appearance and physical signs had not changed and he had the same daily elevation in temperature. Blood cultures were again negative. He was treated with salicylates and after a period of a month his temperature gradually returned to normal. Subjectively he was feeling well, and in spite of advice to the contrary he again left the hospital. During this second longer period under observation, an attempt was made to elicit positive findings of subacute bacterial endocarditis, but no evidence of this disease was found. In the absence of any other source of infection, it was assumed that the patient had an active endocarditis probably superimposed on mitral and aortic valvulitis of rheumatic origin.

August 29, 1926, the patient was admitted for the third time, in acute distress from abdominal pain in the region of the spleen. He stated that after his discharge the previous April, he had worked for a month as a waiter. About the middle of August, or two weeks before this third admission, he awoke in the morning and found that he was unable to move his right arm and noticed some difficulty with his speech. There was no evidence of arthritis. The cardiac findings were the same as noted on previous examinations. The fever now continued elevated to between 38° and 40° C., and the pulse averaged 120 per minute. The patient appeared more pallid than formerly and his blood showed the following: Red blood cells, 3,072,000; white blood cells, 20,000; hemoglobin, 60 per cent. The appearance of embolic phenomena responsible for what was interpreted as a splenic infarct and a cerebral accident, suggested the possibility of subacute bacterial endocarditis. A blood culture taken shortly after admission was found to contain a Gram-negative bacillus. The same organism was obtained repeatedly during the month that the patient lived. The final clinical diagnosis was: Chronic rheumatic mitral disease with stenosis; acute endocarditis of the mitral and aortic valves; cerebral embolus, left hemisphere; infarct of the spleen.

Autopsy Findings. The body is that of a well-developed, somewhat emaciated, white male, aged twenty-two years. The scleræ and skin are of a faint yellow color, and numerous petechiæ are distributed throughout the skin. The right forearm and hand, and both lower extremities are edematous.

The pericardial cavity is completely obliterated by adhesions, which are torn with difficulty. Both pleural cavities contain about 250 cc. of

a clear straw-colored liquid. The leaflets of the pleura on both sides are adherent to one another. The peritoneal cavity, which is smooth and glistening, contains about 400 cc. of a clear straw-colored liquid. The surfaces of all the serous cavities show numerous petechiæ.

Heart: Weighs 550 gm. (with pericardium); the endocardium in general is smooth and glistening. The chordæ tendinæ of the mitral valve are markedly thickened, shortened, and adherent to each other. The leaflets of the mitral valve are thickened, firm, and covered with numerous small, yellowish-gray, friable vegetations. Attached firmly to the base of the aortic leaflet of the mitral valve is a soft, round, reddish-gray thrombus, 2.5 cm. in diameter. The thrombus covers the mitral orifice, leading to a partial occlusion of the valve. The aortic valve leaflets are retracted, rigid and their free margins show several grayish, friable, loosely attached vegetations. The pulmonary and tricuspid valves appear normal. The mitral valve measures 8 cm. in circumference; aortic, 7 cm.; pulmonary, 8 cm.; tricuspid, 12.5 cm. The sinus of Valsalva shows very occasional plaques of plain intimal thickening. The papillary muscles and trabeculæ carneæ are hypertrophic and flattened. These changes, however, are more pronounced in the right ventricle. Both auricles, but especially the left, are dilated and show a thickened wall. The left ventricular wall measures 11 mm. in thickness, right, 5 mm.; left auricles, 1.5 mm.; right, 1 mm. The myocardium on cut section is of a brownish-gray color, and shows the architecture very indistinctly.

Liver: Weighs 2150 gm. The organ shows changes characteristic of cloudy swelling combined with chronic passive congestion.

Spleen: Weighs 950 gm. Organ is markedly enlarged and shows adhesions to the surrounding portions of the diaphragm. The surface contains several yellowish, depressed areas, varying in size from 2 to 12 cm. in diameter. On cut section they are wedge-shaped, of slightly granular appearance, and show a complete loss of normal architecture. The remainder of the spleen is the seat of an acute hyperplasia.

Kidneys: Combined weight 350 gm. No changes other than a cloudy swelling are observed.

The remainder of the organs show no gross pathologic changes.

No permit for removal of the brain was obtained.

Histologic Findings. Heart: The pericardium shows a new formation of connective tissue and an infiltration of mainly lymphocytes, endothelial cells, and a few polymorphonuclear leukocytes throughout. Numerous newly formed vessels are present, filled with red blood cells. The heart muscle fibers are swollen, the cytoplasm is finely granular and shows indistinct striations. No Aschoff's bodies are seen.

Sections of the liver and kidneys show a rather pronounced cloudy swelling

Spleen: Sections show the infarction in addition to marked acute splenic hyperplasia.

Bacteriologic Findings. Several antemortem blood cultures revealed Gram-negative cocci or minute bacilli. The cultures taken in broth flasks were the first five days negative and showed on the sixth day a slight cloudiness. Transplants on agar showed a growth, first after two days and later after an incubation of about twenty hours. The bacilli or cocci were not motile, fermented no carbohydrate, and did not liquefy gelatine. On agar they produced small, translucent colonies. They were strictly aërobic. The patient's serum agglutinated the bacilli up to a dilution of 1 to 1000, while control sera showed no agglutination. Similar bacilli were found in the heart's blood at autopsy. Two rabbits and two guinea pigs were each injected with a suspension of these bacilli in saline. The suspension was made of slant agar cultures with 10 cc. of saline. Rabbit "A" was injected intravenously with 1 cc., and rabbit "B" with 2 cc. Guinea pig "C"

was injected intraperitoneally with 0.5 cc., and guinea pig "D" with 1 cc. Apparently all the animals became very sick a few hours after the injection, took no food, and showed a forced respiration. Two days later they appeared normal. After an interval of fourteen days, rabbit "A" was again injected intravenously with 2.5 cc., and guinea pig "C" with 1 cc., intraperitoneally. Both animals showed similar symptoms. The rabbit died three days after the injection, and at autopsy similar bacilli were cultivated from the heart's blood and the spleen. The guinea pig gradually recovered. The serum of rabbit "A" agglutinated the bacilli up to a dilution of 1 to 3000, while the serum of control rabbits showed no agglutinating power. The bacilli recovered from the patient, as well as from the rabbit, had the characteristics of Brucella melitensis. Through the kindness of Dr. A. C. Evans, Brucella melitensis serum of the melitensis variety and cultures of the abortus and melitensis variety, were obtained. An agglutination of the patient's bacilli with the melitensis serum was positive up to a dilution of 1 to 1600. The patient's serum agglutinated the strain of Brucella melitensis of the melitensis variety up to a dilution of 1 to 800, and the abortus variety up to a dilution of 1 to 1600. To determine the variety of Brucella melitensis in our case, an absorption test was performed. This showed conclusively that we were dealing with the abortus variety of Brucella melitensis.

Summary. The case here reported showed acute superimposed on chronic endocarditis in a patient from whose blood Brucella melitensis of the abortus variety was recovered on several occasions, both ante-mortem and postmortem. The history of rheumatic fever suggests that the endocarditis was rheumatic in origin, but no Aschoff's bodies were found in the myocardium. No source of any other infection was disclosed at autopsy. Though there are recorded cases of endocarditis attributed to Brucella melitensis, there is no proof in our case that the endocarditis was caused by Brucella melitensis of the abortus variety. We, therefore, believe that the case here reported is one of acute and chronic endocarditis associated with Brucella melitensis bacteremia.

REFERENCES.

Evans, A. C.: Studies on Brucella (Alkaligenes) Melitensis, Hygienic Lab. Bull., 1925, **143**.

Sacquépée, E.: Fièvre de Malte ou Mélitococci, Nouveau Traité de Médecine, Paris, 1920.

ACTINOMYCOSIS.

A Report of Five Cases—with Four Autopsies—Two Showing Involvement of the Central Nervous System.

By P. O. Snoke, M.D.,

PHILADELPHIA.

Actinomycosis is one of the rarer interesting diseases. Its protean manifestations make it necessary to rule it out in the diagnosis of abdominal neoplasms, chronic skin and pulmonary infections, and sinuses of osseous origin. The cases we wish to

report exemplify different primary sites. They cover the most frequently seen places of infection.

Distinguished by the misnomer "bovine sarcoma" until 1877, actinomycosis was regarded as a neoplasm. The striking similarity shown between this disease and sarcoma made the differential diagnosis impossible. Bollinger[1] described the ray fungus which he found in the lumpy jaw of cattle as the etiologic factor and a short time later Israel[2] found a similar fungus in certain supposed sarcomata in man. The fact that these were the same organism was proven by Ponfick,[3] in 1882. Since the identification of the disease a considerable literature has appeared. In the past ten years forty-six articles have appeared describing the occurrence of this disease in almost every organ of the body. Certain of these articles are worthy of mention. Brogden[4] reported a series of 14 cases of abdominal actinomycosis, with a mortality of 60 per cent. Only 1 partial autopsy was obtained. Da Costa[5] noted that 50 per cent of the cases he had seen were abdominal. One hundred and seven cases of head and neck actinomycosis were reported from the Mayo Clinic by New and Figi,[6] in 1923, with a mortality of 8.2 per cent. Two cases developed meningeal involvement and 6 cases not included in the mortality statistics had meningeal involvement when first seen.

Case Reports. CASE I.—R. S. was admitted to the Philadelphia General Hospital, June 27, 1923, complaining of pain in the lower right jaw. The pain began in March and gradually grew more severe. In April he noted swelling of the right cheek and a very painful tooth in the lower right alveolus. The pain increased and an abscess developed so he came to the hospital. Past medical history is unimportant. There was no history of trauma. He was a laborer and never lived in the country.

Physically, he was a well-developed negro, aged twenty-two years. On admission to the hospital, the right cheek and submaxillary region were greatly swollen. The mouth could not be opened. The swollen area was indurated (boardlike), red, and a number of fluctuating areas were present. There was marked cervical adenopathy. One month after admission, he developed a psychosis, without any signs of organic brain disease.

On September 6 a number of these fluctuating areas were incised. They drained profusely but other fluctuating areas developed so that an incision and drainage was necessary a few days later (Fig. 1). Smears taken, August 8, were reported positive for actinomycosis. The blood Wassermann was negative. He received two Roentgen ray treatments—the first, one-fourth of an erythema dose, and the second, one-third of an erythema dose, four weeks later. Roentgen ray treatment began, October 28, but had little effect. Copper sulphate solution (25 cc. of 1 per cent solution) was injected.

Potassium iodid by mouth was given to tolerance. He showed, however, no improvement. His temperature was hectic and his pulse ranged between 90 and 120 constantly. The patient became gradually weaker and died, September 11, 1924, fifteen months after admission.

Autopsy. The autopsy was of great interest. The neck was greatly enlarged and showed a number of irregular scars. On the right side, extending from ear to clavicle, were twelve sinuses, all of which appeared to lead to the jaw.

Upon opening the thorax the apex of the right lung was firmly adherent and the first rib was eroded. The necrotic material formed a number of abscesses which involved the apex of the lung. This was a direct extension downward of the disease.

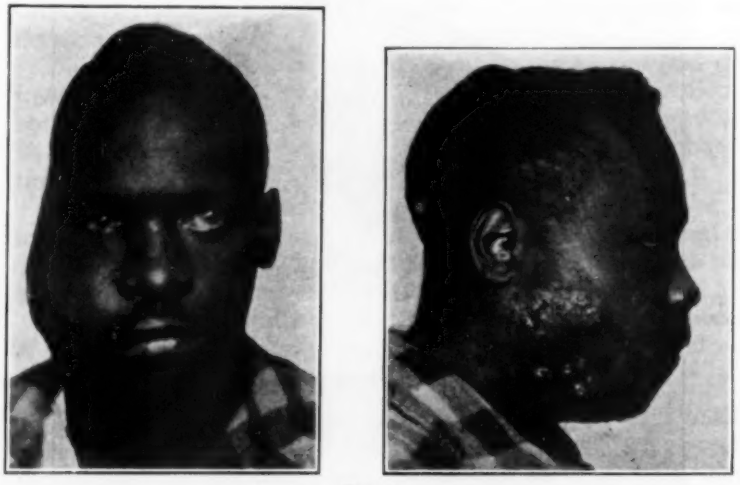


FIG. 1

In the center of the lower lobe of the right lung there was an abscess the size of a hazel nut, full of creamy pus. The other viscera showed nothing of importance. The brain and spinal cord were removed. The spinal cord showed an irregular extradural mass in the lower cervical and upper dorsal region. It seemed to be a plastic exudate and was quite different from tuberculosis or syphilitic pachymeningitis. A diagnosis of extradural abscess of the cord was made. All of these lesions were of actinomycotic origin.

CASE II.—A. S., a white Russian male, aged thirty-six years, came to the Philadelphia General Hospital, November 11, 1922, complaining of pain in the right wrist and lumbar region.

Eight years before, following pneumonia, he developed a pain in his back. This was absent when standing and walking, but sitting,

bending or breathing increased it. Two weeks before admission, he developed pain in the right wrist, with tenderness and marked swelling but no increase in local temperature.

There was a persistent morning cough with blood-tinged expectoration. Night sweats were of frequent occurrence. There was great loss of weight.

Physical examination revealed an anemic, emaciated individual, who was suffering considerable pain. The head and neck showed no noteworthy lesion. The contour of the chest was flat. There were three well-healed scars on the upper chest wall and at the level of the ninth rib on the left side there were a number of draining

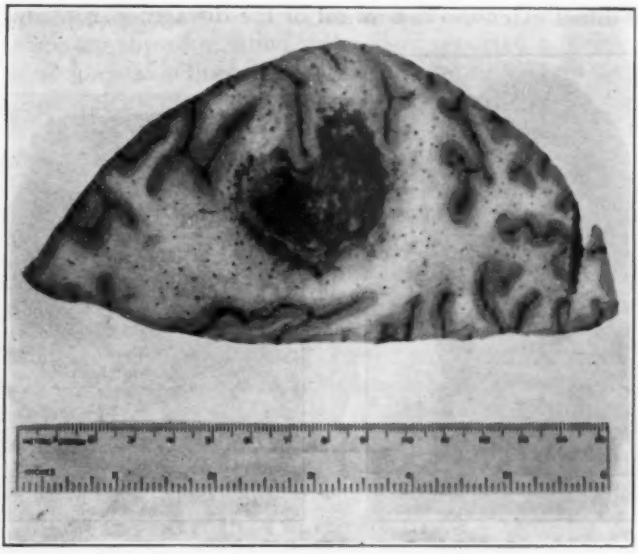


FIG. 2.—Case 2. Actinomycotic abscess of the left cerebrum.

sinuses. The skin about these areas was red and indurated. Percussion revealed dullness at both apices. About the sinuses, the breath sounds were absent. There was a point of tenderness over the third lumbar vertebra. The spine was fixed from the twelfth dorsal vertebra to the sacrum.

A swelling in the left hypochondriac region under the border of the ribs developed, December 22, 1923, and aspiration revealed pus. On December 29 a quart of thick, greenish-yellow foul pus was evacuated through a 2-inch incision in the left lumbar region and a large cavity was palpated. On January 21, a unilateral convulsion occurred. It involved the right arm, face and neck, lasting fifteen minutes. The fingers of the right hand were paralyzed. There then followed daily convulsions and a right hemiparesis. On

January 27 aphasia developed and projectile vomiting followed; the patient died February 2.

The spinal fluid was positive for globulin and showed 74 cells per cubic millimeter. The Wassermann test in the blood and spinal fluid was negative while the colloidal gold read 2223310000. The blood count revealed 10,700 leukocytes, the various elements being within normal limits. Roentgen ray films of the lumbar vertebræ showed marked production of bone about the twelfth dorsal, first, second and third lumbar vertebræ.

Autopsy. The lungs showed active tuberculosis at the right base and left apex. The base of the tongue was removed but histologic section showed no actinomycotic lesions.

In the lower lumbar region on the left side, extending from the twelfth dorsal to the fourth lumbar, there was an abscess cavity varying from 1 to 6 cm. in diameter. The other viscera were negative.

The brain was removed for examination. The skull and dura were normal. On the left side of the brain, there was a distinct bulging in the anterior portion of the parietal lobe. Over an area 10 cm. in diameter there was flattening of convolutions and obliteration of fissures.

On section through this area there was an abscess occupying the left corona radiata and some of the corpus striatum. The contents of the cavity were semifluid. There was a distinctly rough wall, in which granular bodies could be discerned.

The forearm was not examined, but it was felt that an abscess of actinomycotic origin was present. The brain abscess wall showed the ray fungus on histologic examination.

CASE III.—C. F., a young Jewess, was admitted to the Philadelphia Hospital for Mental Diseases, January 8, 1925. Her psychopathic condition was diagnosed: "Manic depressive insanity (manic type)." Her physical examination failed to reveal any evidence of disease. August 25, 1925, she complained of pain in the right side and cough. It was thought that she had an attack of pleurisy. Upon examination a hard nodular lump was found in the right costal region and one in the cervical region of the spine. She was seen by a surgeon, August 30, and transferred to the Philadelphia General Hospital. An attempt was made to remove these nodules surgically under the diagnosis of myofibroma. The specimens sent for histologic study showed chronic suppurative inflammation.

Following the operation the incision failed to heal and yellow pus drained away constantly (Fig. 3). A smear taken November 4, revealed actinomyces. Other masses began to develop in the chest wall, one appeared on the fifth rib, another on the seventh rib in the midmaxillary line and a third on the tenth rib in the midscapular line.

Zinc chlorid applications were made to the suppurating areas,

and 120 gm. of potassium iodid daily were given by mouth. Pregl's iodin was applied locally and injected intravenously. Radium packs were applied February 15, 1926, to a mass in the lower outer quadrant of the right breast and to a mass on the seventh rib in the midaxillary line. The technique advised by New and Figi[6] in their report was used. The lesions improved but unfortunately vertebral involvement occurred. Pain developed in the lower limbs, December 31, 1925. The general course of the disease was unfavorable and a transfusion was given on March 4, 1926. By March 18

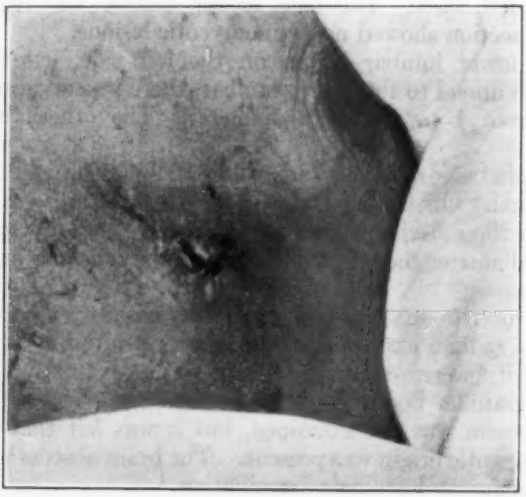


FIG. 3

complete motor paralysis of the left leg had developed and sensation was preserved. There was also partial paralysis of the right leg. No sphincteric weakness occurred. After neurologic examination it was decided to perform a laminectomy for the relief of pain and pressure on the cord. The laminæ of the tenth and the twelfth dorsal vertebræ were resected. The dura and pia were firmly adherent to the cord but no definite pressure or abscess could be located. She failed to improve after operation and died March 26.

Autopsy. At autopsy she weighed only 51 pounds. There were three dark round scars in the right chest wall over the fifth and seventh ribs in the midaxillary line and over the tenth rib in the midscapular line, the size of a dime. In the center of these scars there was ulceration from which a gray, granular, glutinous material could be expressed. An area of inflammation surrounded these ulcers and the skin and subcutaneous tissues in this area were adherent.

The right pleural space was obliterated and the lung could not be removed without tearing. The upper lobe was covered with fibrous, cellular exudate. The middle and lower lobes were fused by adhesions. The lower lobe was densely adherent to the diaphragm which was in turn densely adherent to the liver. The right lower lobe was fibrous throughout, firm and shrunken in size.

In the center of this fibrous lower lobe was a necrotic area the size of a walnut. It contained a gray, red, gelatinous material—flocculent granules. The abscess extended down to the diaphragm.

A very important note was made in the autopsy protocol: "The brain and cord were examined but the brain only showed cortical atrophy. Microscopic section of the spinal cord and meninges shows the meninges infiltrated with round cells of the lymphocytic group." A diagnosis of chronic meningitis was made. Histologic examination of the tissues from the chest and lung lesions confirmed the diagnosis of actinomycosis.

CASE IV.—T. W.,* a weak, dyspneic colored man, aged thirty-eight years, was admitted to the Philadelphia General Hospital, January 16, 1925, complaining of a mass in his abdomen. He was perfectly well until October, 1924, when he began to develop general malaise. This was shortly followed by fever at night and aching in the back. He remained at work as a laborer, unloading fruit boats until December 24. Great weakness and fever finally forced him to stop work. The mass in his side had been present for two months but never pained or bothered him. The past medical history and social history are relatively unimportant.

Physical examination on admission revealed a dyspneic negro, who was extremely anxious to have the mass in his abdomen removed. He had a rapid pulse rate, 120 to 130 per minute, and probably a relative mitral insufficiency. Right hydrothorax was present. The abdomen was protuberant and contained a mass which lay in the upper left quadrant. It extended forward to the midline and down to the pelvic brim. As to whether it was attached to the anterior abdominal wall, clinicians could not agree. The edge of this mass was irregular but did not show typical notching. The mass moved with respiration. There was no generalized adenopathy. The clinical course while in the hospital was afebrile. The pulse remained rapid, respirations 25 per minute. Laboratory examinations included: Blood Wassermann test negative. Blood chemistry normal. Blood count: Red blood cells, 3,700,000; white blood cells, 23,000; hemoglobin, 9 gm. per 100 cc. Gastric analysis showed no free acid and total acidity within normal limits. Blood was present in every tube. Roentgen ray examinations gave the following information: Esophagus negative; stomach negative, but pushed

* Reported from the Radiologic Department of the Philadelphia General Hospital by the courtesy of J. B. Carnett, M.D.

to the left by an extrinsic mass. The duodenum was not visualized. There was some enlargement of the cecum. The large intestine was full of barium at the end of the twenty-four-hour period. Chest negative. Later films showed the right kidney shadow in normal position but the left obscured by a mass. Diagnosis: Extrinsic mass in the upper left abdomen.

Exploratory laparotomy was decided upon. On February 12, 1925, under gas anesthesia the abdomen was opened. The patient expired on the table. Stimulation and artificial respirations were without avail. Cardiac massage was ineffectual.

Autopsy. At autopsy a large mass of scar tissue was found involving the splenic flexure and descending colon, almost obliterating the lumen. It was fixed to the anterior abdominal wall and infiltrated the left rectus muscle. The lumen of the bowel showed no ulceration. This fibrous mass when incised contained many sinuses full of greenish-yellow pus. The abdomen showed no other marked pathology. The heart was markedly dilated on the right side but showed no other noteworthy lesions. Lungs and pleura showed no noteworthy lesion.

Sections were taken from the abdominal wall directly overlying the mass and the muscle showed marked degenerative changes. Smears and sections showed the ray fungus.

CASE V.—J. C.,* a herdsman, aged sixty years, was troubled with a sore tongue which he first noticed in the early part of December, 1926. No attention was paid to it until December 18, when the increase in size and pain on mastication forced him to see a doctor. He was referred to the Radiologic Department the following day with a questionable diagnosis of malignancy. Examination of the tongue on December 21 showed in the left edge of the tip a large nodule. It was the size of a chestnut and purplish-red in color. The center of it seemed necrotic, exuding yellowish pus. Toward the midline, there was a somewhat similar but smaller lesion (Fig. 4). These lesions were stony hard but seemed well circumscribed. They did not present the whitish indurated condition seen in early carcinoma of the tongue nor was there typical ulceration with rolled edges seen in carcinomatous ulcers. Pressure on the larger nodule produced a small drop of pus and a smear was taken. There were glands palpable in the submental and sublingual regions. This patient's teeth showed many caries and much pyorrhea. Laboratory examination revealed a negative Wassermann, while the smear taken from the pus on the tongue showed actinomyces. The blood count was normal. There was no leukocytosis.

Surgical diathermy was decided upon as the proper treatment for the local lesion. The anterior portion of the left half of the

* Reported from the Radiologic Department of the Philadelphia General Hospital by the courtesy of G. M. Dorrance, M.D.

tongue was excised with the diatherm under chloroform anesthesia on December 30. The lingual artery was ligated. No attempt was made to suture the tip of the tongue into the incision. The mucous membrane of the floor of the mouth and the dorsum of the tongue were sutured together. The patient made an uneventual recovery and was discharged February 10, 1927. He received potassium iodid to the limit of tolerance while in the hospital, also small quantities of mercury and atropin. A series of twelve Roentgen ray treatments extending from January 11 to February 10 to the right and left sides of the neck were given. The factors were: two minutes, 5 ma., nine inch spark gap; 5 mm. aluminum; 50 S.T.D.

FIG. 4.

The pathologic tissue removed at the time of operation showed mycelia and signs of chronic inflammation. At our last observation, June 14, 1927, the patient was perfectly well. The nodes in the neck were smaller but still palpable.

Comments. These 5 cases illustrate very well the seriousness of actinomycosis. Other reports have minimized the danger of this disease. From our experience with Case III in treating these lesions in the skin with radium, we quite agree with New and Figi,[6] of the Mayo Clinic, in their method of treatment and excellence of result. The spreading of the disease beyond the area treated is the factor of supreme importance. It was this feature of the disease which originally made observers consider it a sarcoma. The involvement of the vertebræ as seen in Case II was regarded as metastatic. The paths by which actinomycosis disseminates are not well known. From our observation of these 5 cases we would consider direct extension along the lymphatics as the most probable method. In Case I, lymphatics explain everything except the small isolated

abscess in the center of the lower lobe of the right lung. This could well be explained by aspiration. It might, however, have been through the venous system.

We must most certainly view the abscess in the brain of Case II as the result of blood embolism. The primary site of this case seems to have been the vertebræ. What part the pneumonia, eight years before we saw him, played in the onset of this disease, we do not know. It is hardly conceivable that actinomycosis should remain quiescent for eight years, although there is some evidence that it may. It does seem probable when considering Case IV that infection may enter through the intestine without causing a mucosal lesion which would be discoverable at autopsy. In the case of abdominal actinomycosis infection could not have occurred except through the intestine as there was no skin lesion or history of a skin lesion on the abdomen.

Case I presents a textbook picture of actinomycosis involving the jaw and would be analogous to what has been described in cattle as "lumpy jaw," whereas Case V would be described in veterinary medicine as "wooden tongue."

It is interesting to note the frequency of central nervous system lesions in this group of five cases. Case I presents an extradural abscess. Case II presents a brain abscess. Case III showed a chronic meningitis but from the sections examined the pathologists were unable to ascertain whether or not this was of actinomycotic origin.

Summary. 1. Five cases of actinomycosis are presented starting in: (*a*) Jaw; (*b*) chest wall and lung; (*c*) vertebræ and lung; (*d*) abdomen; (*e*) tongue.

2. In two of these cases definite involvement occurred in or about the central system. In a third case chronic inflammation was present but actinomycotic origin could not be proven.

3. The diagnosis is most easily made from a smear by the finding of "sulphur" granules and the ray fungus under the microscope.

4. Radium and Roentgen ray therapy are considered of great therapeutic value in treating skin lesions or lesions in close proximity to the skin.

5. Iodids should always be administered to tolerance.

6. Free drainage should always be afforded by surgical means if the temperature indicates retained pus.

7. Actinomycosis should be considered of a very serious nature and be treated with all the therapeutic agents at our command.

BIBLIOGRAPHY.

1. Bollinger: Centralbl. f. d. med. Wissensch., 1877, **34**, 789.
2. Israel: Virchow's Arch. f. path. Anat., 1879, **24**, 15; 1879, **27**, 421.
3. Ponfick: Die Actinomyklose und Menschen, Berlin, 1882.
4. Brogden: J. Lab. and Clin. Med., 1922, **8**, 180
5. Da Costa: Modern Surgery, 9th ed., 1925, p. 254.
6. New and Figi: Surg., Gynec. and Obst., 1923, **36**, 617.

CARCINOMA OF THE ESOPHAGUS.

A Report of Fifty Cases.

By Julius Sherman, M.D.,
San Francisco, Calif.

(From the Department of Medicine, Stanford University Medical School.)

Most cases of cancer of the esophagus have been classed as medical cases until the patient was about to die from food and water starvation, cachexia and metastasis. Failure to make an early diagnosis has been due to several factors. Many of us have not recognized that esophagoscopy is not infallible in establishing the diagnosis. In this paper I am emphasizing those cases in which the cancer grows outward toward the submucosa and is not recognized by the endoscopist. Another misleading situation is that in which an esophagitis is set up around the seat of the cancer and is mistaken for the actual lesion. In either case, following a negative biopsy report, if indications of cancer of the esophagus are present, the esophagoscopy and biopsy examination must be repeated. (Cf. Emperor Frederick's cancer of the larynx.)

The following 2 cases illustrate the importance of not relying upon a negative esophagoscopic and biopsy report when indications of cancer of the esophagus are present.

Case Reports.—Case I.—Mrs. M. D., aged forty-one years, came to the gastrointestinal clinics, August 24, 1926. She was born in Scotland, where she worked in shops until her marriage, five years ago. She has had no children and no miscarriages. Has always taken hot tea, six to eight cups daily.

She has had indigestion since the age of fourteen years. As far back as the age of twenty years she remembers having difficulty in swallowing. She recalls the sensation of food sticking in her throat and seeming not to reach her stomach. This was especially true of solids. This condition grew steadily worse and for the past eight months she has had dysphagia and has been forced to live on liquid diet. Of late she frequently vomited fifteen to twenty minutes after eating. The vomitus, in which blood was never noticed, consisted of food just eaten. She lost 10 pounds within the last eight months.

Physical examination was essentially negative, except that all her teeth had been extracted. Laboratory tests showed a hemoglobin of 87 per cent (Sahli); red cells 4,200,000; Wassermann negative; urine and stool examinations negative. Stomach contents: Total acidity, 50; free hydrochloric acid, 40. The gall bladder was visualized normally by the intravenous method with tetraiodo- phenolphthalein. Roentgenographic examination revealed an uneven

narrowing in the esophagus, suggesting an ulceration about 7 cm. above the esophageal opening in the diaphragm. About 3 cm. below this there was a herniation of part of the cardiac end of the esophagus through the diaphragm.

An esophagoscope was passed to a distance of 52 cm. The mucous membrane was friable, congested and bled easily. A well-defined, nodular indurated mass, elevated about 3 mm. was found 25 to 27 cm. from the upper incisors. It bled easily on contact with the esophagoscope. There was no difficulty in passing the instrument beyond the mass into the stomach. The cardiac orifice was found at 33 cm., it was very lax as was also the esophagus just above. The esophagoscope was passed about 4 cm. into the stomach when it came in contact with the stomach wall. The stomach appeared normal. The first biopsy report was negative, but the specimen taken one week later from the upper part of the growth showed ulcerating adenocarcinoma of the esophagus.

On November 2, 1926, an exploratory thoracotomy was performed by Dr. Emile Holman. The lesion of the esophagus was found inaccessibly located posterior to the hilum of the left lung surrounded by dense deposits of abnormal fibrous tissue. Further procedure was abandoned.

Since the operation the patient has gained in weight and for the most part is able to swallow solid food easily. Roentgenogram taken March 5, 1927, showed the same obstruction of the esophagus.

Case II.—Mr. A. M., aged forty-nine years, a butler, native of Scotland, came to the gastrointestinal clinics on August 6, 1926, complaining of difficulty in swallowing, especially solids, and pain in the front chest.

The patient was well until a year ago, when he began having dull pain in the region of the right nipple. It was present constantly, but did not keep him awake at night. He had had a cough for many years which became worse with the onset of the pain. He lost no weight and felt no worse until four months ago, when he noticed that on swallowing the pain was increasingly severe, being felt when the food reached the lower end of the esophagus.

Esophagoscopic examination had been done elsewhere on July 7 and was reported to show cardiospasm, and a roentgenogram revealed a constriction at the cardia. Shortly the patient began to have difficulty in swallowing, especially solids. At this time he was forced to remain on liquid and semisoft diet. A second esophagoscopy by a different operator failed to show any lesion of the mucosa. He began to lose in weight and his cough grew worse, night sweats setting in. He now became cyanotic, expectorated more profusely a greenish, bad-tasting, foul-smelling sputum.

In the physical examination the essential findings were as follows: Teeth in poor condition, tactile fremitus increased over the left

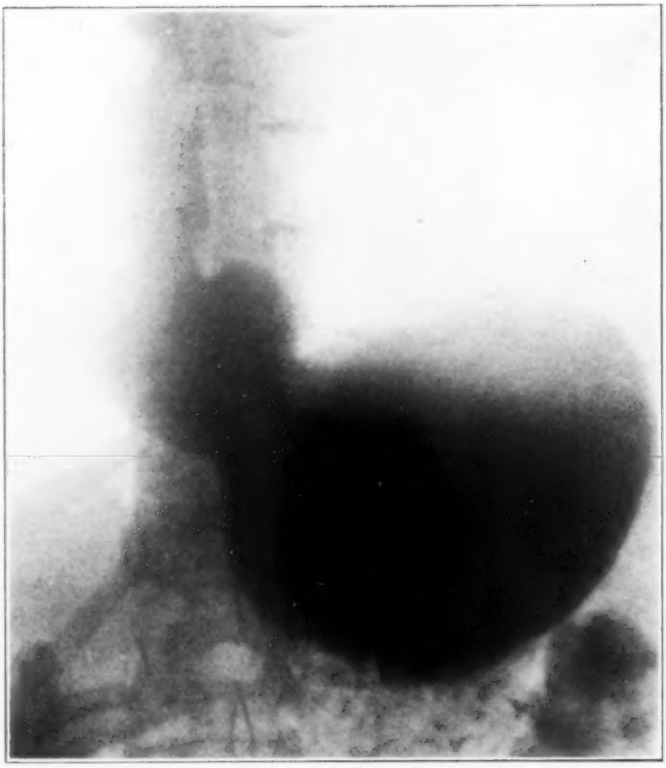


FIG. 1.—Case I. Showing nodular intrusion on the lumen of the esophagus 5 cm. above the cardia. There is a considerable herniation of the cardiac end of the stomach through the esophageal opening in the diaphragm.

FIG. 2.—Case II. Showing ulcerated constriction of the esophagus for a distance of about 5 cm. at the level of the bifurcation of the trachea. Definite dilatation is evident above this, but fluid runs past it fairly readily.

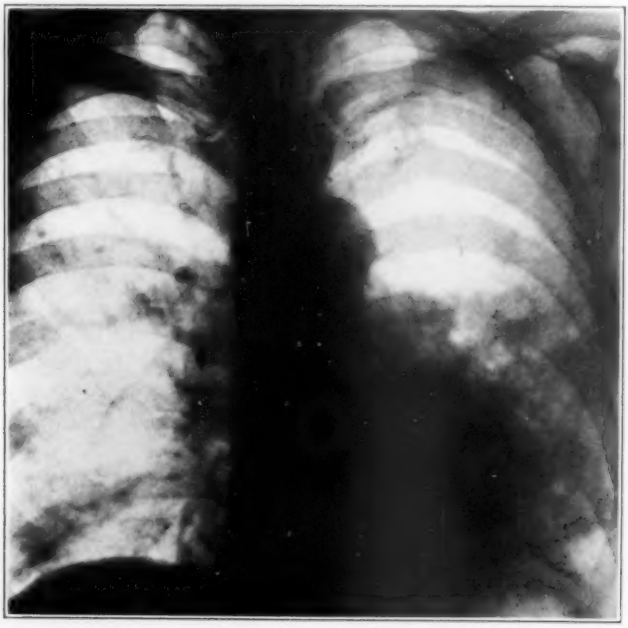


FIG. 3.—Case II. Leakage of barium from esophagus into left bronchus through bronchoesophageal fistula.

lung below the scapula. Percussion note was impaired at the left base and also between the scapula and the vertebræ. Breath sounds were decreased at the right base and seemed to be increased at the left base. Friction rubs were heard at the left base and occasional râles at the right base. The heart was normal.

With the exception of the clubbing of the fingers, the rest of the examination was normal.

The laboratory tests showed: Red cells, 4,860,000; hemoglobin, 84 per cent (Sahli); white blood cells, 9920; polymorphonuclears, 63 per cent; Wassermann negative, urine and sputum negative. Culture of sputum showed growth of hemolytic and nonhemolytic streptococci.

On October 15 the Roentgen ray examination of the chest and gastrointestinal region was made. The hilum shadows were increased on both sides. Areas of fuzzy density in the left lower lobe were interpreted as being due to a low-grade pneumonic consolidation or pneumonitis, secondary, possibly to leakage through an esophageal-bronchial fistula, although no barium was seen to go into this fistula in the fluoroscopic examination. A constriction was seen about the middle of the esophagus, irregular in outline and with a slightly dilated pouch above it. The barium cream was held up here only temporarily. The stomach was normal in position, tone and flexibility. The remainder of the gastrointestinal series was negative.

Esophagoscopy and bronchoscopy at this time showed ulcerating lesion of the main bronchus and esophagus and this was interpreted as probable primary bronchial carcimona with perforation into the esophagus.

On November 22 the esophagus was again Roentgen rayed and revealed the following: The barium passed down the esophagus to a point at the level of the bifurcation of the trachea. From this point the left main bronchus was immediately visualized and the ramifications of the lower bronchial tree were filled. After the film was taken, the patient was reëxamined fluoroscopically. The barium was seen to be distributed throughout the left lower bronchial tree. The whole left chest was filled with a cottony mottling, undoubtedly the result of food passing from the esophagus into the bronchial tree. It was concluded that this was due to an esophageal-bronchial fistula, bilateral, localized in the primary bifurcation.

The patient grew progressively worse and died suddenly on November 27.

The necropsy confirmed the diagnosis of cancer of the esophagus with perforation into the left bronchus and complicated by bronchopneumonia of the left lung.

Now it is evident from a study of these 2 cases that the early symptoms were not heeded and that an early diagnosis was difficult to establish. In Case I the cancer extended toward the submucosa

and very little of it protruded into the lumen of the esophagus. This condition caused an esophagitis, which was misleading to the endoscopist and resulted in a negative biopsy report in spite of the fact that the Roentgen ray strongly suggested carcinoma of the esophagus. The biopsy from the second esophagoscopy revealed the cancer.

In Case II a similar condition existed, the growth extending outward toward the left bronchus, even perforating it and forming an esophageal-bronchial fistula. Three different endoscopists examined the esophagus in various stages of the disease without arriving at the correct diagnosis, the first two finding no intrinsic lesion.

Of the 50 cases of carcinoma of the esophagus on which this paper is based 37 were subjected to esophagoscopy. In 9 of these, including the 2 just cited, this examination did not establish the diagnosis, but on the contrary the tissue removed contained no neoplasm. In other words in almost 25 per cent of the cases this procedure did not aid, but was actually misleading in establishing the diagnosis. This does not detract from the value of the endoscopy but shows how carefully the examination must be made and its results interpreted. Repeated examinations may be necessary to demonstrate the lesion.

Summary and Conclusions.—1. Although carcinoma of the esophagus is of comparatively slow growth and for a long time a purely local process, the thoracic surgeon has made little progress in its cure because it is rarely seen by him in its early stages.

2. Dysphagia, always considered in textbooks as an early symptom, is in reality a late symptom. This is especially true of the cases in which the growth beginning deep in the mucosa, grows excentrically. These do not have large indurations or annular constrictions until late.

3. The earliest symptoms are nervousness in swallowing, and a feeling of the food sticking and finally going down, which must emphatically be considered as symptoms of possible malignancy. Intermittent dysphagia is present in all cases of esophageal cancer at some stage.

4. Roentgen ray examination and esophagoscopy are the most reliable methods of diagnosis in the early stages. By means of the esophagoscope the endoscopist can examine every portion of the esophagus and can obtain tissue for biopsy.

5. There are cases in which the malignancy grows outward toward the submucosa and the endoscopist fails to reveal it. Often, an esophagitis occurs in the region of the lesion and the endoscopist mistakes this condition for the cancerous growth. In either case, if other indications strongly suggest the presence of carcinoma of the esophagus, the esophagoscopy and biopsy must be repeated as shown in 25 per cent of the cases reviewed.

6. Erroneous diagnosis may be due to dependence on inferential instead of objective evidence or to the antiquated and even dangerous use of the bougie as a diagnostic aid. A diagnosis of neurotic condition is frequently made in the early stages of cases that have later been proven to be cancer of the esophagus. Another common error is to make a diagnosis of spasm after a history of intermittent stoppage of food with normal intervals.

7. The only hope for the cure of cancer of the esophagus lies in early resection, the technique of which is being developed by the thoracic surgeon. Life has been prolonged by a combination of early gastrostomy, proper food by tube, plenty of water by mouth and deep Roentgen ray treatments. The cure by radium is very questionable, yet there may have been some palliation in a few cases.

STATISTICAL REPORTS OF FIFTY CASES OF CANCER OF THE ESOPHAGUS FROM THE MEDICAL CLINICS OF STANFORD UNIVERSITY MEDICAL SCHOOL.

Age	Average age, 56.5 yrs.; youngest, 37 yrs.; oldest, 77 yrs.
Sex	Females, 4 (8 per cent); males, 46 (92 per cent).
Complaint	Dysphagia in 44 cases (88 per cent).
Loss of weight	Average loss of weight, 32.5 pounds in 40 cases recorded; maximum loss, 80 pounds; minimum loss, 8 pounds.
First symptoms	Substernal oppression and pain, 9 cases (18 per cent); queer feeling in swallowing, 7 cases (14 per cent).
Feeling of obstruction at lower end of esophagus	In 30 cases (60 per cent).
Difficulty in swallowing solid food periodically	In 43 cases (90 per cent).
Duration of symptoms	43 cases (86 per cent) reviewed: average duration, 8.5 mos.; shortest duration, 1 mo; longest, 7 yrs.
Complications	Cough in 13 cases (26 per cent); vomiting and regurgitation in 11 cases (22 per cent).
Roentgenologic examination	46 cases (92 per cent) confirmed the diagnosis made clinically by esophagoscopic examination of cancer of the esophagus.
Esophagoscopy	37 cases (60 per cent) esophagoscoped and tissue thus obtained for biopsy.
Anatomic lesion	First portion of esophagus, 3 (6 per cent); second portion, 2 (4 per cent); third portion, 30 (60 per cent).
Blood picture	30 cases; highest hemoglobin, 100 per cent; lowest hemoglobin, 40 per cent; red blood cells: highest, 5,000,000; lowest, 3,000,000.
Biopsy	In 26 cases (52 per cent) biopsy reports were positive for cancer of the esophagus; 2 cases (4 per cent) only, biopsy reports were negative for cancer; in 9 cases (25 per cent) first biopsy reported negative and second biopsy definitely positive for cancer.
Treatment	7 cases (14 per cent) were given deep Roentgen ray therapy; 6 cases (12 per cent) received radium therapy; 8 cases (16 per cent) had gastrostomies.
Necropsy	10 cases (20 per cent) came to necropsy.

BIBLIOGRAPHY.

Brickner, W. M., and Milch, H.: Pathologic Fracture of Humerus Due to Carcinoma Metastatis from a Silent Growth in Esophagus, Internat. Clin., 1926, **1**, 207.

Cabot, R. C.: Carcinoma of Esophagus with Metastases in Liver and Various Glands, Cabot Case 12061, Massachusetts General Hospital, Boston Med. and Surg. J., 1926, **194**, 257.

Coplin, W. M. L.: Injury, Inflammation, Irritation, Known Causes of Cancer; Their Recognition the Only Safe and Sound Basis of Prevention, J. Am. Med. Assn., 1922, **78**, 1523.

Dean, L. W.: Coëxistent Carcinoma, Tuberculosis and Syphilis of the Esophagus, Ann. Otol., Rhinol. and Laryngol., 1917, **26**, 619.

Hanford, C. W.: Radium Technique in Treating Cancer of the Esophagus, J. Am. Med. Assn., 1922, **78**, 9.

Hirsch, I. S.: The Roentgen Ray Study of the Esophagus, Interstate Med. J., 1916, **23**, 24.

Jackson, C.: Carcinoma and Sarcoma of Esophagus: Plea for Early Diagnosis, J. Radiol., 1925, **6**, 485.

Jackson, C.: Why Does Not the Thoracic Surgeon Cure Cancer of the Esophagus? Arch. Surg., 1926, **12**, 236.

Jones, J. A.: Some Clinical Observations on the Lingual Tonsil, J. Laryngol. and Otol., 1923, **38**, 465.

Pancoast, H. K.: *X*-ray The Diagnosis of Surgical Diseases of the Esophagus, Surg. Clin. North America, 1924, **4**, 34.

Patterson, E. J.: Cancer of the Esophagus, Pennsylvania Med. J., 1919, **23**, 147.

Pfahler, G. E.: The Diagnosis of Esophageal Stricture, Arch. Diag., 1909, **2**, 44.

Stone, W. S.: Radium Therapy in Carcinoma of the Esophagus, Arch. Surg., 1926, **12**, 230.

Torek, F.: Surgical Treatment of Carcinoma of the Esophagus, Arch. Surg., 1926, **12**, 232.

Turner, A. L.: Carcinoma of the Postericoid Region and Upper End of the Esophagus, J. Laryngol. and Otol., 1920, **35**, 34.

Wassink, W. F.: Radium Treatment of Cancer of Esophagus, Abstract, J. Am. Med. Assn., 1926, **86**, 1669.

THE DIAGNOSTIC VALUE OF DUODENAL DRAINAGE IN GALL-STONE DISEASE.

With Special Reference to the Significance of So-called Bilirubin Calcium Pigment.

By G. M. Piersol, M.D., H. L. Bockus, M.D.,

and

Harry Shay, M.D.,

Philadelphia.

(From the Gastrointestinal Clinic of the Graduate School of Medicine, University of Pennsylvania.)

So much has been written of duodenal drainage since Lyon's original paper claiming gall-bladder evacuation by this method, that one hesitates to write further on the subject without some claim to originality. The purpose of this paper is to emphasize the importance of the examination of bile sediment in particular,

and bile drainage generally in the diagnosis of gall-stone disease. This, in spite of the recent introduction of cholecystography, which, in our opinion, does not supplant duodenal drainage. We have not included an exhaustive review of the literature of this subject with which all workers in this field are doubtlessly familiar. The literature already contains many such complete reviews. Theoretically one has at present ample experimental evidence to conclude that bile from the gall bladder can be obtained by duodenal drainage. The concentration function of that organ has been established by Rous and McMaster[2] and confirmed by Mann and Bollman,[3] Graham and his associates,[4] Milliken[5] and Whitaker and many others. That the gall bladder empties itself through the cystic duct has been satisfactorily shown by Mentzer,[6] Abramson,[7] Whitaker,[8] Winkelstein and Aschner[9] and others. Winkelstein and Aschner, and Silverman and Menville,[10] have experimentally obtained gall-bladder contents through the duodenal tube following the intraduodenal instillation of magnesium sulphate. The time has passed when theories, unsupported by scientific proof, can be accepted to explain the phenomena of the appearance of dark concentrated bile in the duodenum. The above experimental evidence fortified by clinical experience make the theories based merely upon fancy untenable.

TABLE I.—FINDINGS IN FIFTY-SEVEN SURGICALLY PROVEN CASES OF GALL-BLADDER DISEASE.

Cholelithiasis, 46 cases; noncalculous cholecystitis, 11.
Age varied from twenty-six to seventy-one years; average age, forty-eight years.
White, 54; colored, 3.
Males, 14; females, 43.
Married females, 36; 18 had average 3 pregnancies.

	Number of cases.	Per cent.
Typhoid fever	6	10.5
Previous appendicitis	6	10.5
Analysis of 46 stone cases:		
History of colic	22	47.8
History not pointing toward gall-bladder disease	24	52.2
Tenderness under right costal margin	16	34.7
Tenderness diffuse over abdomen	3	6.5
History of colic and local tenderness	12	26.1
Gastric analysis:		
Acidity (24 cases):		
Hyperacidity	8	33.3
Normal acidity	9	37.5
Hypoacidity	7	29.2
Motility (22 cases):		
Hypermotility	7	31.8
Normal motility	13	59.2
Delayed motility	2	9.0
Bile (22 cases):		
Bile regurgitation	12	54.6
No bile	10	45.4

A series of 57 cases of gall-bladder disease (Table I), proven by operation or autopsy, are reported. Forty-six were cases of chole-

lithiasis and the remaining belong to the so-called noncalculous cholecystitis group. Three of this latter group had definite pericholecystic involvement. The age of the patients varied from twenty-six to seventy-one years, the average age being forty-eight years. Fifty-four of the patients were white and 3 colored. The usual preponderance of gall-bladder disease in the female sex was shown; 43 of our cases were females, or 67 per cent. Of the 43 female cases 7 were single and 36 were married. Eighteen of the married women had gone through one or more confinements. The habitus was noted in 30 cases. Fifteen, or 50 per cent, were hypersthenic; 10, or 33 per cent, sthenic; 5 cases were of the asthenic build. A history of typhoid fever was present in 6 cases. A similar number gave a history of previous appendicitis.

Of the 46 surgically proven gall-stone cases 22 gave a history which was typical or somewhat suggestive of gall-bladder colic. A history of previous attacks of jaundice was obtained in 5 cases. Three had icterus on admission; 52.2 per cent had symptoms which were not suggestive of disease of the gall bladder. Tenderness at the right costal margin was present at sometime during observation in 19 cases. But in 3 of these parietal tenderness was so generalized over the abdomen as to negative the likelihood of the gall bladder being the sole cause. Of these stone cases 58.7 per cent had no tenderness in the usual situation of the gall bladder. Only 12 cases had both colic and tenderness. The majority of these cases were referred to the Gastrointestinal Clinic of the Graduate School Hospitals because they presented difficulties in diagnosis. This accounts for the low incidence of symptoms and signs suggesting gall-bladder disease. It is likely that the number of cases with local manifestations would have been less were it not for the reference of certain typical cases at our request in order to have opportunity to test the value of several diagnostic procedures which will be discussed.

A mention of gall-bladder tenderness would not be complete without drawing attention to the recent papers of our colleague, Dr. J. B. Carnett,[11] on the simulation of intraäbdominal lesions by the pain and tenderness of parietal (intercostal) neuralgia. Our observations coincide with Carnett's in that a considerable number of patients having tenderness in the biliary region do not have gall-bladder disease. Carnett's simple bedside tests for differentiation between visceral and parietal tenderness shoul be employed in every case which exhibits any abdominal tenderness. He has demonstrated that the usual method of palpation over relaxed abdominal muscles fails to reveal the parietal location of tenderness due to intercostal neuralgia with the unfortunate result that the tenderness is erroneously ascribed to a visceral lesion. In every case in which tenderness is encountered he advises repeating the palpation while the patient holds the abdominal muscles as tense as possible either

by forcibly depressing the diaphragm or by actively raising and holding the feet from the bed with knees extended. The tense abdominal muscles prevent elicitation of true intraäbdominal tenderness. The tenderness found by palpation over tense muscles is always parietal in location and therefore must not be regarded as evidence of visceral disease. Parietal neuralgia is a very common affection and its distribution is often so widespread that Carnett's contention that it cannot conceivably be due to Head's viscero-parietal reflex in most instances seems justifiable. We can also confirm Carnett's observation that excision of a definitely diseased gall bladder commonly fails to cure a coincident intercostal neuralgia. The parietal location of tenderness can further be demonstrated by firmly pinching a fold of skin and fat of the biliary region between the thumb and first two fingers and then comparing the sensitiveness of a similar pinch of the corresponding area on the opposite side of the midline. Associated with the tenderness of the abdominal parietes, some tenderness will frequently be found along the intercostal nerve trunks by making pressure between the ribs. Tenderness of the parietes has been encountered quite commonly in our routine abdominal examinations. We feel confident that the usual examination of the abdomen does not take it into account. Caution should be observed in attributing right costal margin tenderness to a diseased gall bladder. Carnett[11] has shown that a characteristically positive Murphy test of hooking the fingers under the right costal margin during forced inspiration is frequently due to either the diffuse tenderness or a "tender point" of parietal neuralgia in the absence of gall-bladder disease and even after cholecystectomy. We have found that a "tender point" of intercostal neuralgia has frequently been mistaken by a consultant for localized biliary tenderness and that at operation the gall bladder was far removed from the site of tenderness. Carnett very properly points out that the difficulties of diagnosis of gall-bladder disease are greatly intensified by the presence of intercostal neuralgia in the biliary region and that Roentgen rays, cholecystograms and biliary drainages must be employed for diagnosis. He scoffs at the commonly expressed statement that the diagnosis of gall-bladder disease is easily determined by the history and the usual bedside examination without further diagnostic aids. We agree with Carnett that the routine examination of the abdomen for tenderness is of little value in the diagnosis of chronic gall-bladder disease, unless the patient is examined during an acute exacerbation.

Fractional gastric analysis was carried out on 24 cases. In 33.3 per cent (8 cases) there was hyperacidity; 37.5 per cent (9 cases), normal acidity; 29.2 per cent (7 cases), hypoacidity. There were no cases of true achylia gastrica, although in several instances no acid appeared until sixty or ninety minutes after the test meal. The motility of the stomach in most cases was normal or slightly

increased. There were 7 cases of hypermotility, 13 of normal motility and 2 cases of delayed emptying. Bile regurgitation into the stomach was also recorded. Bile was absent in all fractions in 10 cases. Three had bile only in the fasting residuum, 2 cases had bile in one fraction other than the fasting and in 7 instances bile was present in more than one fraction. The number of cases having fractional gastric tube studies is too small to attempt to evaluate the significance of biliary regurgitation. The blood count revealed normal findings except in 3 cases, in which slight anemia was present. The blood cholesterol was recorded in 14 of the stone cases. The average figure was 166 mg. per 100 cc., ranging from 130 to 210 mg. per 100 cc. Six cases had figures above 170 mg. per 100 cc. Of 7 noncalculous cases the blood cholesterol ranged from 104 to 255, with an average of 176 and 3 of these had figures above 170. It will be noted that there is little difference in the blood cholesterol level in the calculous and noncalculous group, but that the average figure is a trifle above normal. The futility of attempting to estimate the diagnostic significance of blood cholesterol from so few observations seems obvious.

TABLE II.—FINDINGS IN FORTY-SIX SURGICALLY PROVEN CASES OF CHOLELITHIASIS.

Duodenal tube findings in 42 cases.	Number of cases.	Per cent.
(*a*) Cholesterin alone	4	9.5
(*b*) Characteristic pigment	4	9.5
(*c*) Cholesterin and pigment	23	54.8
(*d*) Cholesterin or pigment or both	31	73.8
"B" bile absent in (*d*)	6	19.3
(*e*) No cholesterin or pigment	11	26.2
Absent gall-bladder function at operation (*e*)	7	63.6
Absent "B" bile (*e*)	9	81.8
Cases without local symptoms with cholesterin or pigment	17	40.5
Other microscopic data:		
White blood cells	2	5.0
Columnar epithelium	9	21.4
Bile-stained mucus	4	9.4
Gastrointestinal Roentgen ray (18 cases):		
Stones visualized	1	5.5
Gall-bladder visualized	1	5.5
Adhesion defects	5	27.5
Oral cholecystography (19 cases):		
Normal	1	5.0
Faint visualization	3	16.0
Delayed emptying (small)	1	5.0
Not visualized	15	79.0
Stones visualized	6	32.0
Hepatitis	12	25.2
Pancreatitis (enlargement and hardening)	11	24.0

Duodenal Tube Findings in 42 Surgically Proven Cases of Cholelithiasis (Table II). Although there is an abundance of literature pertaining to the diagnosis of various types of gall-tract disease based upon duodenal-tube examination, there is very little of a

concrete nature concerning the diagnosis of gall-stone disease. A survey of the literature on this subject to our surprise shows little reference to the diagnostic value of certain elements found in bile, namely, cholesterin crystals and bilirubin pigment. Hollander[12] refers to finding cholesterin crystals in several cases of proven gall-stone disease. His report covers the duodenal tube findings in 17 operated cases of gall-bladder disease. Mateer and Henderson[13] reported a series of 23 stone cases upon which duodenal tube studies were performed. The bile removed from the bladder at operation disclosed cholesterin crystals in 17. One-sixth of them were associated with calcium crystals. Thirty-five per cent of these cases had cholesterin crystals in the bile obtained from the duodenal tube before operation. Approximately 26 per cent of their proven stone cases had cholesterin crystals in the bile obtained from the duodenum preoperatively. No reference is made to any type of pigment crystal by the above writers. Einhorn,[14] in several articles, mentions both cholesterin crystals and bilirubin pigment as a finding of importance in the fasting duodenal bile in stone cases. Jones,[15] in a very comprehensive survey of a large series of stone cases makes reference to the frequent finding of cholesterin and calcium bilirubinate as obtained by the Lyon test. While there are many other references to the presence of pigment in the bile as obtained by duodenal tube, no attempt at classification of such pigment has been made. We wish to stress the diagnostic importance of a pigmentary deposit which we have found frequently associated with gall stones. This pigment appears as a lustrous, golden-yellow, more or less granular precipitate. The color varies from a pale yellow to a deep orange. There is no other element in bile which can be mistaken for it, in its typical morphology and physical characteristics. It is this pigment which we have called bilirubin calcium pigment.* Jones, from his illustration and description, is undoubtedly referring to the same pigment. He calls it calcium bilirubinate, although as far as we have been able to learn no definite chemical identification of this pigment has been forthcoming. It is likely, particularly in view of Rous'[16] recent contribution, "The Cause of Gall-stone Formation," that this pigment is some combination of bilirubin and calcium, and may very well be called calcium bilirubinate or bilirubin calcium pigment until definite identification is possible. Any experienced bile microscopist is undoubtedly familiar with a large number of precipitated elements which have been called pigment. These substances range in color from red to black and often have a mahogany-brown cast. Morphologically they are subject to numerous variations. Various workers have attributed the appearance of such elements to cholelithiasis, sand, gall-bladder stasis, inflammation, and so forth. We have been unable to attribute to this group of substances any definite diagnostic import. We do not know their

* [Compare Aschoff's combination (cholesterin pigment calcium) stone.—Ed.]

identity, and mention them only to avoid conflict with the classical pigment above described. Confusion is often added by finding associated with this type of dark-brown substance a number of irregular, thick, clear crystals. In many such instances we have found fibers resembling cellulose and vegetable hairs intimately mixed with the so-called pigment deposit. Even small fragments of rubber from the duodenal tube may prove annoying to the inexperienced, as they resemble somewhat the brown pigment just described.

In our series of 57 cases subjected to gall-bladder operations cholesterin crystals alone were found in the bile by duodenal drainage six times. Four of these cases had stones at operation. One had subacute cholecystitis with the strawberry type of mucosa. The other was a doubtful case of chronic cholecystitis. Bilirubin calcium (calcium bilirubinate) was found alone in the bile from the duodenum on 6 occasions. Four of these cases likewise proved to have stones, another unquestionably had chronic cholecystitis and the sixth had recently recovered from obstructive jaundice. Cholesterin crystals and bilirubin calcium pigment were found in combination in 23 of the 42 stone cases. Gall stones have been present in every case operated upon so far in which cholesterin crystals and bilirubin calcium was discovered in the bile before operation. Of the stone cases 73.8 per cent showed either one or both of these elements in the bile preoperatively. In Jones' series of 42 surgically proven cases cholesterin was found in 3, calcium bilirubinate in 24 cases and the combination of both in 14, or 97 per cent, as compared to our 73.8 per cent.

These crystalline and pigmentary elements were almost invariably found in the dark fraction of bile. Not infrequently in stone cases difficulty is encountered in evacuating a "B" fraction. Often two or more stimulations, or even several drainages, will be necessary before a dark fraction of bile is obtained. A careful search in this delayed type of "B" bile will often reveal the above-mentioned pathologic elements. The advantage of magnesium sulphate or other stimulating substances applied to the duodenum is obvious when the above observation is borne in mind. In our experience crystalline elements were found in the duodenal aspirate before stimulation in only a small number of cases. Another observation worthy of note is the color of the bile containing bilirubin calcium pigment. In about 50 per cent of these pigment cases the "B" fraction had a brick-brown color.

Only 11 of our stone cases which were drained preoperatively failed to have cholesterin crystals or pigment (26.2 per cent). Of these 63.6 per cent (7 cases) had absent gall-bladder function at operation and 81.8 per cent (9 cases) had absent "B" bile by duodenal drainage. Only 2 stone cases of those drained (42 cases) having a

"B" fraction of bile failed to show cholesterin or characteristic pigment. This may explain the discrepancy in percentage of positive findings of cholesterin crystals and calcium bilirubin in the stone cases between our series and that of Jones. It is conceivable that he was successful in obtaining bile from the gall bladder in a larger number of cases. It may be well to mention at this time that 17 cases of gall stones (40.5 per cent) without local symptoms had cholesterin crystals or characteristic pigment when drained diagnostically.

Cellular elements were rather infrequently encountered during microscopic examination of the bile of the stone cases. Bile-stained pus cells, so often present in pathologic cases, were conspicuous by their absence in this group. They were seen in only 2 cases, or 5 per cent. Tall columnar epithelial cells, described by Lyon as a common finding in cases of cholecystitis, were found in but 9 of these stone cases (21.4 per cent). The bile contained strands of bile-stained mucus in 9.4 per cent of cases. We were impressed by the lack of cellular and inflammatory elements in the calculous group. An explanation may possibly be found in the number of cases reported by pathologists, in which a section of the gall bladder showed marked atrophy or denudation of the mucosa. We scraped the mucosa of the excised gall bladder in a number of cases in an effort to obtain pavement epithelium. In most instances cells could not be found in the scrapings.

Giardia (lamblia) intestinalis were recovered in 4 of the 50 cases studied by the tube method (8 per cent). These cases all belonged to the lithiasis group.

Gall-bladder Function by Bile Drainage Compared with Operative Findings. Of the series of 57 cases of surgically proven gall-bladder disease 50 were subjected to nonsurgical biliary drainage. Thirty of the 50 cases drained were found to have bile in appreciable quantity in the gall bladder at operation. In all but 3 of these cases a "B" fraction of bile was obtained through the duodenal tube. A persistence of gall-bladder function in these stone cases as gauged by duodenal drainage was corroborated at operation in 90 per cent of the cases. The remaining 20 cases which were drained had no bile in the gall bladder at operation, and gross disease existed which could be assumed to account for the complete absence of gall-bladder function. We failed to obtain dark bile in all but 3 of these cases. In 1 of them the bile was described as mixed "BC," and was not a definite "B" fraction. However, we included this case as having "B" bile. The duodenal tube finding of absent gall-bladder bile was confirmed at operation in 85 per cent of cases. Summing up, the reliability of duodenal drainage as a gauge of gall-bladder function in cases of gall-bladder disease, 88 per cent of our preoperative findings in this respect were confirmed at operation.

TABLE III.—COMPARISON BETWEEN BILE DRAINAGE AND CHOLECYSTOGRAPHY IN CASES SHOWING PERSISTENT GALL-BLADDER FUNCTION AT OPERATION.

Bile drainage.	Cholecystography.		Gall-bladder content at operation.
	Visualization.	Stones.	
40 cc. (light brown)	None	0	Ample bile; stones.
100 cc.	Normal	0	Viscid bile; sand.
20 cc.	None	0	Small amount of bile; stones.
90 cc.	Faint	0	Normal bile; stones.
60 cc.	None	0	Blood and bile; stones.
No definite "B"	None	0	Bile present; stones.
40 cc.	Normal	0	Normal bile.
30 cc.	Faint	0	Bile present; stones.
30 cc.	Normal	0	Normal bile.
Normal	None	0	Bile present; stones.
60 cc.	Normal	0	Bile present.
None	None	0	Small amount of bile; stones.

No visualization in 6 cases. Five had stones. Faint visualization in 2 cases. Both stones. "B" bile present in all but 2 cases. Bile drainage better criterion of function of gall bladder although all cases except 1 showing faulty visualization had stones.

Comparison between Bile Drainage and Cholecystography in Cases Showing Persistent Gall-bladder Function at Operation (Table III). This comparison was made in 12 cases. Of these the oral cholecystography failed to visualize the gall bladder in 6 cases. In 4 of the 6 cases with no visualization a "B" fraction of bile was obtained from the duodenum. In 1 of the 4 only 20 cc. of "B" was recovered. Two cases had faint shadows following the administration of the dye. A normal quantity of bile was present at operation in one, in which case 90 cc. of "B" bile was obtained by duodenal drainage. The other case with faint visualization was found to have some bile at operation and a rather small "B" fraction (30 cc.). In the 4 remaining cases normal function was found to be present both by drainage and cholecystography. It would seem from this small number of cases that bile drainage is a better criterion of the function of the gall bladder in these pathologic cases as the percentage of error in cholecystography was 50 per cent as compared with an error of 16.6 per cent by duodenal drainage. An analysis of this group shows 8 stone cases, none of which had stones visualized by the cholecystographic method, and in 7 of them cholesterin crystals and pigment were obtained from the bile sediment by duodenal drainage. This emphasizes in a striking way the value of this finding of cholesterin crystals and pigment as compared with cholecystographic study in the diagnosis of gall-stone disease. It is interesting to note that in the 4 cases having no visualization, but having "B" bile by drainage, cholesterin and pigment were found preoperatively. One must be forced to consider that bile can be obtained from the gall bladder by drainage in a fairly large percentage of cases in which visualization is absent, otherwise it would

be difficult to account for the presence of cholesterin and pigment in these cases.

TABLE IV.—COMPARISON BETWEEN BILE DRAINAGE AND CHOLECYSTOGRAPHY IN CASES SHOWING ABSENT GALL-BLADDER FUNCTION AT OPERATION.

Bile drainage, "B" bile, number of drainages.	Cholecystography.		Operative findings.			
	Visualization.	Stones.	Bile present, cc.	Lack of function due to:		
				Ob. cys. d.	Filled stones.	Gross disease.
None (3)	Normal, small	+	5	..	+	+
10 cc.	Faint	+	5	+	+	
50 cc. (light)	None (2)	0	5	..	+	+
None (3)	None (2)	0	0	+	+	
None	None	0	0	+	+	
None	None	+	5	+	+	
None	None	+	5	..	+	
None (7)	None	+	0	+	+	+
None	None	0	0	..	+	
	None	+	5	±	+	
	None	0	0	+	+	+(Ca)

"B" present in 1 case and visualization in 2 cases having gross dysfunction at operation.

Comparison between Bile Drainage and Cholecystography in Cases Showing Absent Gall-bladder Function at Operation (Table IV). This comparison was made in 9 cases. The oral cholecystographic method failed to visualize the gall bladder in 7 cases. One had a faint shadow and one a very small shadow. These 2 cases both had a very small quantity of bile at operation, but so little that they were better classified as absent function cases. The drainage likewise revealed absent "B" in all but 1 case, in which 50 cc. of a light "B" (?) fraction was secured. When the gall bladder had ceased to function such lack of function was indicated by both cholecystography and tube findings. Since it has been revealed in the preceding group (Table III) that "B" will frequently be found in the absence of visualization by oral cholecystography, we feel that bile drainage repeatedly and intelligently performed is a better criterion of gall-bladder function. Eleven cases of stones without gall-bladder function were cholecystographed. Six (54.5 per cent) had either positive or negative shadows of stones, 4 of them in non-visualized gall bladders, indicating that bile is entering the gall bladder but not in sufficient amount or concentration to cast a shadow of the gall bladder, confirming our previous observations in the preceding paragraph. In 4 of these cases the diagnosis was made by actual visualization of stone shadows. These 6 cases of

positive visualization of stones by this method occurred in a series of 19 stone cases (including the cases with persistent gall-bladder function), representing 32 per cent visualization of stones by this method. This might be compared with a positive finding of cholesterin and pigment in 73.8 per cent of the stone cases. This percentage may not represent the true state of affairs. There is no way of determining the percentage of cases having stones in which we obtained negative tube findings. However, this error could not be great because of the corollary diagnostic methods which were used in all doubtful cases. Our percentage of confirmed diagnosis is necessarily high because we were rarely satisfied with negative findings after one drainage in the suspicious case. Of the 34 stone cases in which this data was available, in 9 instances more than one drainage was necessary before cholesterin crystals and characteristic pigment was obtained. An average of three drainages was necessary to obtain positive microscopic findings in these 9 cases. In those cases showing pathologic elements in the first drainage 9 cases required more than one stimulation, an average of two and seven-tenths stimulations being necessary.

Gastrointestinal Roentgen Ray Findings in 18 Stone Cases (Table II). Stones were visualized without the administration of dye in 1 case. In only 1 instance was the gall bladder itself visualized. Marked irregularities resembling those often seen in adhesions were found in the stomach or duodenum in 5 cases (27.5 per cent). These defects were of the minute incisura variety; definite subtraction from the outline of the shadow cast by the opaque meal. They were not necessarily persistent, but when present in one position were shown on all film exposures in that position. Films taken on the upright patient are more apt to show such deformities. These defects are usually in the distal 2 inches of stomach or duodenal bulb, probably more often in the stomach and in most instances on the lesser curvature, although they may be seen on either curvature. At times this characteristic type of defect is seen: two small identical incisuras on the same curvature within 1 or 2 cm. of each other. We have observed these defects not infrequently in gall-bladder cases, although definite data could only be obtained in 5 of this series. There seems to be a tendency to ignore such defects and ascribe them to temporary spasm, drag from gastroptosis, etc. In every instance so far where we have had opportunity to confirm at operation defects of this type we have found the cause to be adhesion from the gall bladder.

Hepatitis and Pancreatitis at Operation. Note was made of the condition of the pancreas at operation in most cases. Five of the stone cases had slight hardening of the head of the pancreas and 6 had, in addition, appreciable enlargement. Twenty-four per cent had gross lesions in the pancreas. Of the 46 cases of cholelithiasis the surgeon reported evidence of local hepatitis in the region of the

gall bladder in 12 cases. Two cases had slight enlargement of the liver and one cirrhosis. Liver involvement was present in 33 per cent of cases. We have not found any of the present liver function tests of much value in diagnosing such liver dysfunction. In this group of cases practically normal liver function was the rule.

Conclusions. An analysis of 57 proven cases of gall-bladder disease (46 cases of gall stones), we believe, warrants the following conclusions:

1. A characteristic pigment, the so-called bilirubin calcium pigment or calcium bilirubinate, has been found in the bile drained from the duodenum with sufficient constancy to give it significance in the diagnosis of gall stones. We feel that this pigment is distinct from and should not be confused with other elements found in bile commonly referred to as pigment.

2. Of the 42 cholelithiasis cases that were drained pre-operatively, 73.8 per cent showed this pigment or cholesterin or both in the bile obtained from the duodenum. All of the cases having both cholesterin crystals and pigment in the bile obtained by biliary drainage proved to be cases of gall stones. In the majority of cases these elements were only found in the dark or "B" bile.

3. In only 35 per cent of proven gall-stone cases were the stones visualized by oral cholecystography, whereas in the same series a pre-operative diagnosis of stones was made from duodenal tube findings in 47 per cent of cases.

4. A pre-operative estimate of gall-bladder function from the duodenal tube examination proved correct in 88 per cent. On the other hand, a similar estimation by oral cholecystography was found correct in only 65 per cent of cases.

5. We feel justified in reëmphasizing the value and importance of properly carried out duodenal biliary drainage in the diagnosis of gall-stone disease. We believe that it has not been supplanted by any other diagnostic procedure.

NOTE.—We are indebted to Dr. George Vaughan, of Wilmington, Del., for allowing us to include 9 of his cases of proven gall-bladder disease.

BIBLIOGRAPHY.

1. Lyon, B. B. V.: Diagnosis and Treatment of Diseases of the Gall Bladder and Biliary Ducts, J. Am. Med. Assn., 1919, **73**, 980.
2. Rous, P., and McMaster, P. D.: J. Exp. Med., 1921, **34**, 47.
3. Mann and Bollman: J. Lab. and Clin. Med., 1925, vol. **10**.
4. Graham, E. A., Cole, W. H., and Cophir, G. H.: Cholecystography: An Experimental and Clinical Study, Ann. Surg., 1925, **84**, 14.
5. Milliken, G., and Whitaker, L. R.: The Clinical Use of Sodium Tetraiodophenolphthalein for Cholecystography, Surg., Gynec., and Obst., 1925, **40**, 464.
6. Mentzer, S. H.: Proceedings of American Association of Pathologists and Bacteriologists, 1925.
7. Abramson, H. A.: . Proc. Soc. Exper. Biol. and Med., 1923–1924, **21**, 407.
8. Whitaker, L. R.: J. Am. Med. Assn., 1926, **86**, 239.
9. Winkelstein, A., and Aschner, P. W.: AM. J. MED. SCI., 1925, **169**, 679.
10. Silverman, D. N., and Menville, L. J.: J. Am. Med. Assn., 1925, **84**, 416.

11. Carnett, J. B.: Surg., Gynec. and Obst., 1926, **42**, 625; Annals of Surgery, 1927, **86**, 747.
12. Hollander, E.: Experiences with Nonsurgical Biliary Drainage, Am. J. Med. Sci., 1923, **156**, 497.
13. Mateer, J. G., and Henderson, W. S.: Chronic Biliary Tract Diseases: The Diagnostic Criteria, Arch. Int. Med., 1926, **38**, 708.
14. Einhorn, M.: On Gall Stones, Med. Rec., April 2, 1921; The Importance of the Direct Examination of Bile in the Diagnosis of Gall-bladder Lesion, Med. J. and Rec., 1924, **120**, 9, 60.
15. Jones, C. M.: The Rational Use of Duodenal Drainage, Arch. Int. Med., 1924, **34**, 60.
16. Rous, P., McMaster, P. D., and Drury, D. R.: Observations on Some Causes of Gall-stone Formation: Experimental Cholelithiasis in the Absence of Stasis, Infection and Gall-bladder Influences, J. Exper. Med., 1924, **39**, 77.

USE OF FASTING DONORS IN BLOOD TRANSFUSIONS.

A Preliminary Report.

By Walter V. Brem, M.D., A. H. Zeiler, M.D.,

and

Roy W. Hammack, M.D.,

Los Angeles, Calif.

(From the Clinical Laboratory of Brem, Zeiler and Hammack, Los Angeles, Calif.)

Based upon our experience with more than four thousand transfusions, we have recognized three types of transfusion reactions as follows: (1) Febrile reactions, with or without chills; (2) wrong-group reactions; (3) anaphylactoid reactions.

Wrong-group and anaphylactoid reactions are similar in that their onset is shortly after the beginning of a transfusion, they are accompanied by substernal distress, backache, a feeling of fullness in the head, suffusion of the face and eyes, and a condition of collapse. They differ in that the former are followed by hemoglobinuria, and the latter usually present the symptom of urticaria. Both of these reaction types are rare.

The common type of reaction is that first mentioned, the febrile reaction. Excluding reactions due to citrated, defibrinated or otherwise treated blood, a considerable percentage of whole-blood transfusions are followed by more or less fever, sometimes chills, and general malaise. Since 1916, we have used almost exclusively the Lindeman[1] syringe-whole-blood method, substituting needles for cannulas. In nearly all our transfusions, we have given to adults approximately 500 cc. of blood, but occasionally we have used two or three donors and doubled or trebled the amount.

Since we have given transfusions for the medical profession at large and have not been, ourselves, attending physicians, our records

of reactions are not sufficiently full for statistical purposes. We should judge, however, that among more than four thousand transfusions with the syringe-whole-blood method, about 20 per cent were followed by a febrile reaction of 1° or more. Most of these reactions caused no great discomfort and no apparent injury to the patient, but occasional ones were severe, and actually or potentially harmful. For example, following a transfusion reaction, a splenic anemia patient's leukocytes fell from about 5000 to 800 per c.mm., and the platelets decreased so markedly in number that we feared purpura hemorrhagica might supervene. In other words, the bone marrow seemed to be hard hit by the reaction. It would seem to be most desirable, therefore, in transfusing certain patients to eliminate these reactions if possible.

Kordenat and Smithies[2] have reviewed recently current theories advanced to account for transfusion reaction. In studying the theories relating to febrile reactions, one is impressed by their highly speculative character, and by the fact that there is no tangible experimental evidence supporting them, nor do they assist one in avoiding the reactions.

Transfusions of Blood from Fasting Donors. A recent experience led us to believe that the use of fasting donors is at least one important method of avoiding febrile reactions.

A patient, white, American, male, aged fifty years, had had a duodenal ulcer for twenty-six years. He had had a gastrojejunostomy performed about sixteen years ago, and he seemed practically well for ten years, when, for the first time, a hemorrhage occurred, January 14, 1920. His hemoglobin dropped from 93 per cent to 54 per cent in three days, when he was given a transfusion of 500 cc. of whole blood by the syringe method. The patient belonged to Group III (Moss[3] classification), and a Group III nonfasting donor was used. The patient's temperature began to rise after about twelve hours, and it fluctuated between 100° and 103° for three days; there was great malaise and prostration, and annoying premature systoles occurred for the first time. After forty-eight hours, a thrombus developed in the vein at the site of the transfusion, and the vein was painful and tender for a week. This thrombus completely disappeared in time, and the normal patency of the vein was restored. The hemorrhage seemed to be checked by the transfusion, blood gradually disappeared from the stools, and by February 18, 1920 the hemoglobin had risen to 88 per cent. A Roentgen ray showed the gastrojejunostomy opening still patent without indication of ulcer. There was a well-marked filling defect of the duodenum.

The patient was in good condition until July 4, 1923, when another hemorrhage in three days reduced his hemoglobin to 50 per cent. A transfusion similar to the first, using a nonfasting donor, seemed to check the hemorrhage immediately, for a clear line of demarkation was seen between the tarry portion and the light yellow portion

of a stool voided the following day. But again a distressing reaction occurred. It began about twenty-four hours after the transfusion, and lasted for four days. The maximum temperature was only 101.2°, but it was accompanied by severe malaise, prostration, premature systoles, and, again, by thrombus formation in the vein at the site of the transfusion. This thrombus, also, disappeared entirely in time. The thrombus formation in this patient was the first that we had encountered in about 2000 transfusions. We have encountered it in several other patients since then, in one repeatedly, in the others once each when the transfusion was unusually prolonged, due to technical difficulties.

Our patient again made a good recovery, and remained in good condition until a third hemorrhage, beginning during the night of December 10, 1925, brought his hemoglobin down to 51 per cent in three days. He objected to transfusion this time because of the former severe reactions. The hemorrhage ceased spontaneously, and the tarriness of the stools gradually cleared. The hemoglobin rose slowly, but on February 25, 1926 it had reached only 76 per cent, its highest point before the next hemorrhage, and the bleeding time was slightly prolonged, being six minutes.

On the night of March 4, 1926, a fourth hemorrhage began, the stools were tarry on the morning of March 5, and the hemoglobin had dropped already to 60 per cent. In the hope of checking quickly the hemorrhage, a transfusion was agreed upon. Thinking that possibly a reaction could be avoided by using a "universal donor," the patient was transfused from a Group IV donor (nonfasting) and 500 cc. of blood was given about 2 P.M. A chill occurred about half an hour afterward, there was considerable malaise and prostration, and the temperature rose to 101.2°. There was slight fever and malaise on the second day, none on the third. No definite thrombus formed but the vein wall seemed thickened and was tender.

The hemorrhage did not cease and the hemoglobin continued to fall until on March 10 it was 29 per cent, and the patient's condition was growing alarming. On that day, another transfusion of 500 cc. of blood from a Group III donor was given at 5 P.M. The patient's condition improved and his hemoglobin rose from 29 to 39 per cent, but a mild reaction began with a slight chill five hours afterward, the temperature reached only 99.4°, and there was slight malaise. The next day the reaction was over, and we hoped that the patient had become "desensitized" and could bear future transfusions without distress.

On March 12, two days later, a third transfusion of 500 cc. from a Group III donor was given at 5 P.M. A rather severe reaction began with a chill in three hours, the temperature rose to 101.2°, and there was considerable malaise and prostration. On the second day, there was slight fever and malaise; none on the third day,

The vein wall became tender and thickened, but without definite thrombus formation. The hemoglobin rose from 39 to 49 per cent, and the patient's condition was much improved.

On the night of March 14, there seemed to be a recurrence of the hemorrhage. The patient felt weaker on March 15, his pulse was more rapid, and his hemoglobin had dropped back to 42 per cent. On the next day, the patient was better and his hemoglobin was 45 per cent.

There was considerable discussion at this time regarding further transfusions. The reaction following the third transfusion indicated that the patient was not "desensitized." Everybody dreaded further transfusions on account of the reactions, and the patient would not consider an operation because of his stormy convalescence from abdominal operations on two former occasions, and his doubtfulness about the result.

All of us were cudgeling our brains for possible explanations of the reactions when it was suggested that they might be due to toxic products of digestion in the donor's blood, and that possibly they could be avoided by having a donor fast for a certain length of time before the transfusion. The reactions were not unlike those resulting from the injection of proteoses for nonspecific protein shock. It was agreed to try out the theory, and a Group III donor was instructed not to eat anything after dinner the night before the transfusion.

The fourth transfusion (500 cc.) was given at 9 A.M., March 16. We were delighted that there was not the slightest indication of a reaction. On March 17, the hemoglobin had risen from 45 before the transfusion to 53 per cent, the patient's condition was excellent, and he was insisting upon another transfusion immediately.

The fifth transfusion (500 cc.) was given, using a similarly fasting donor, on March 18, and again there was not the slightest reaction. The hemoglobin rose from 53 to 60 per cent on March 19. But on March 20, the hemoglobin was only 57 per cent.

The sixth transfusion (250 cc.) was given, using another Group III fasting donor, at 9 A.M., March 20. The donor in this transfusion suffered from a vagus inhibition of the heart, he became pale, his blood pressure fell, and his vein ceased to fill sufficiently fast with blood enough to feed the syringes. After a prolonged attempt, the transfusion was discontinued when half the usual quantity had been given. Not the slightest systemic reaction occurred, but the vein became much thickened and tender. It later cleared up completely.

On the morning of March 22, the patient's hemoglobin was still only 57 per cent, the red corpuscle count was about 200,000 less, the patient did not feel so well, and his pulse was a little accelerated. Another recurrence of the hemorrhage was feared, and as the patient himself wished to test the theory of reactions, and did not wish to permit possible bleeding to continue without a transfusion

until the following morning, a transfusion that afternoon was agreed upon. A Group III donor was instructed to eat a hearty luncheon including beef steak.

The seventh transfusion (625 cc.) was given on March 22 at 3 P.M., two hours after the Group III donor had eaten as he had been instructed to do. At 5 P.M., two hours after the transfusion, there was a slight chill, malaise, increased pulse rate, and fever rising to 102.6°. The experiment seemed to give striking evidence in favor of the theory, until at 6 P.M. it was noticed that the patient's urine was dark red and contained a heavy sediment. Tests showed that the urine contained hemoglobin and albumin. No red corpuscles were seen, but there were numerous heavy black granular casts similar to those seen in malarial hemoglobinuria. The hemoglobinuria had ceased by the following morning. The albumin and casts slowly decreased and disappeared within a few days. The hemoglobin rose to 61 per cent immediately after the transfusion, but fell back to 58 per cent on March 25.

This reaction was very disconcerting. It was an ordinary febrile reaction in every respect excepting the hemoglobinuria, which we had never seen in reactions other than those due to wrong grouping. On the other hand, wrong-group reaction had always occurred immediately, and we had not seen or heard of one with an onset delayed as long as two hours. Furthermore, we rechecked the grouping of the donor with Groups II, III and IV sera and corpuscles, and cross-checked the patient's and donor's bloods by the microscopic method described by Brem.[4] The patient's serum caused the donor's corpuscles to form rather unusually marked rouleaux, but these did not seem to be true clumps. Macroscopic preparations made by Moss's[3] technique and incubated overnight showed no agglutination or hemolysis, and microscopic examination of these preparations showed no rouleau formation. The donor had been used once before for a Group III patient and there had been no reaction. Further, the corpuscles of the donor used in the fifth transfusion showed rouleau formation as well-marked. How, then, was this reaction to be interpreted, and what was its significance in relation to further transfusions?

It was suggested that the repeated transfusions at short intervals had produced a condition of hypersensitization to Group III corpuscles resulting in an erythrolytic reaction. This theory was rejected, however, as it seemed contrary to established facts regarding sensitization and desensitization phenomena, *i. e.*, the repeated transfusions at short intervals should have been an ideal procedure for desensitizing one who had previously acquired an anaphylactic sensitization.

It seemed that either toxic products of digestion in the donor's blood included an erythrolytic substance, or else the donor belonged to one of Guthrie and Huck's[5] subgroups with amboceptors and recep-

tors so few that no definite agglutination or hemolysis appeared in testing with the patient's serum and corpuscles. Evidence that perhaps supported the latter view might be seen in the fact that after the rise of hemoglobin immediately following the transfusion, the percentage gradually decreased until it returned to the pretransfusion figure. This fall of hemoglobin might have been due to the destruction of the injected corpuscles. But, on the other hand, it might have resulted from the continued oozing of blood from the ulcer.

Finally, we decided that the reaction did not contraindicate further transfusions. We felt troubled, however, over the indefinite results of the group testing in this case, and we determined, therefore, to use Group IV donors for further transfusions.

The eighth transfusion (500 cc.) was given with the blood of a fasting Group IV donor on March 26, 1926 at 10 A.M. At 6 P.M., eight hours after the transfusion, the patient felt slightly chilly and uncomfortable, and his temperature rose to 99.6°, which was maximum. It was normal the following morning. There was no hemoglobinuria. The reaction was very mild. The hemoglobin rose from 58 to 71 per cent and remained at 71 per cent until April 1, 1926.

A ninth, and last transfusion was given on April 1, 1926. The blood injected (375 cc.) was transferred from a fasting Group IV donor. There was not the slightest reaction of any kind. The hemoglobin rose from 71 per cent before transfusion to 78 per cent on the following day. It continued to rise gradually afterward until it reached 90 per cent about April 23, 1926. The patient regained rapidly his strength, weight and general health.

Discussion. The evidence from the above case seems to indicate that there was some toxic substance, to which the patient was sensitive, in the blood of the nonfasting donors used in the first three transfusions of the fourth hemorrhage, and that the toxic substance was not present in the blood of four fasting donors, used in subsequent transfusions, and but small in amount in a fifth fasting donor. The reaction in which hemoglobinuria appeared after a transfusion from a nonfasting donor who had eaten a hearty protein meal, while interesting and suggestive, is anomalous and difficult to interpret. It is our belief that the protein meal was related at least to the febrile phase of the reaction.

Whether or not toxic products of digestion in donors' bloods may account for many of the general reactions following transfusions is a problem which may be approached by clinicians from one of two angles, each of which presents difficulties.

1. Two large series of transfusions, one with nonfasting and one with fasting donors, may be studied and the reactions compared The two series should contain only afebrile cases, the whole blood without anticoagulants should be given by the same technique,

transfusions with fasting and nonfasting donors would best alternate, and the donors' diet should be carefully controlled. Obviously the investigation by this method would be long, tedious and difficult, and the result equivocal.

2. Patients who require multiple transfusions, and who have reacted with chills and fever to transfusions with whole, untreated blood from nonfasting donors, may be considered as indicators of toxic substances in the blood of donors. The reactions of such patients when fasting donors are used will furnish experimental evidence for or against the theory. This method of approach is much the better one, we believe. But such patients will be found only by accident, and they will not be numerous.

We, ourselves, have tested fasting donors twice in one other case. The patient was a man suffering from pernicious anemia; he had had repeated transfusions from nonfasting donors, several times from two donors, each giving 500 cc. of blood; and he had had severe chill-and-fever reactions with considerable malaise after each transfusion. He was transfused three times from fasting donors and he still had a febrile reaction each time, but the chill and malaise were much less marked. Unfortunately, he was not a good experimental case for he had a temperature varying from 99° to 100° before each transfusion. Such a patient probably has an unstable heat mechanism and, probably, his thermic reactions could not be relied upon. However, we mention the case for what it is worth as evidence opposed to the theory that the use of fasting donors may prevent reactions.

If it should be shown definitely that substances toxic for certain sensitive patients occur in the blood of apparently healthy donors shortly after eating, a number of interesting questions would be suggested. For example, what is the nature of the toxic substances and have the donors themselves achieved complete tolerance for them; do the donors vary in their tolerance or in the quantity of the substances they absorb; and may the less tolerant ones suffer from degenerative diseases such as nephritis, cirrhosis of the liver, myocarditis and arteriosclerosis? What foods or what kinds of protein food are precursors of the toxic substances? How long should the donor fast, and should the fasting be absolute or should proteins only be excluded?

Summary and Conclusions. 1. A patient with duodenal ulcer suffered from recurrent hemorrhages, to combat the effects of which he was given transfusions of blood.

2. When transfusions were given from nonfasting donors, the patient had rather severe febrile reactions.

3. When fasting donors were used, he had no reactions from four transfusions, and only a mild reaction from a fifth.

4. On one occasion when a transfusion was given two hours after the donor had eaten a hearty protein meal including beef steak,

the patient had a severe chill-and-fever reaction beginning two hours after the transfusion. Three hours after, hemoglobinuria was observed. No error in grouping of the bloods could be discovered.

5. The evidence from this case suggests that some of the febrile reactions following transfusions may be due to toxic products of digestion in the nonfasting donor's blood, and that such reactions may be avoided by having donors fast for a certain period of time before the transfusion. In our case, an overnight fast seemed to be sufficient.

NOTE.—Since this paper was written, Doan's[6] paper on incompatible leukocytes as a cause of transfusion reactions has been published. It may be that the "digestive leukocytosis" following a protein meal causes or enhances reactions by increasing the number of incompatible leukocytes. However, in our case it would seem to be stretching the bounds of coincidence to suggest that the leukocytes were incompatible in the first three transfusions and the seventh transfusion with nonfasting donors, while they were compatible in the five transfusions with fasting donors. It may be that both factors, toxic products of digestion and incompatible leukocytes, may act independently or together to produce or enhance reactions.

REFERENCES.

1. Lindeman, E. E.: J. Am. Med. Assn., 1919, **72**, 1661.
2. Kordenat, R. A., and Smithies, F.: J. Am. Med. Assn., 1925, **85**, 1193.
3. Moss, W. L.: Bull. Johns Hopkins Hosp., 1910, **21**, 63.
4. Brem, W. V.: J. Am. Med. Assn., 1916, **67**, 190.
5. Guthrie, C. G., and Huck, J. G.: Bull. Johns Hopkins Hosp., 1923, **34**, 37, 80.
6. Doan, C. A.: J. Am. Med. Assn., 1926, **86**, 1593.

BILE PIGMENTS AND BILE ACIDS OF THE BLOOD IN JAUNDICE.*

BY HOWARD F. SHATTUCK, M.D., ICHIRO KATAYAMA, M.D.,

AND

JOHN A. KILLIAN, PH.D.

(From the Department of Medicine, and the Department of Laboratories, New York Post-Graduate Medical School and Hospital.)

BILE pigment metabolism has been the subject of numerous contributions to the literature within recent years, both from the clinician and the experimentalist. Much of this work has been stimulated by the elaboration of dependable quantitative methods for the bilirubin of the blood serum and for urobilin of the urine. Clinicians have been ever on the alert to apply these methods to human cases for purposes of differential diagnosis or as a guide to therapeutic measures. The metabolism of the bile acids, however, in normal individuals and in pathologic conditions still remains

* Read before the American Gastro-Enterological Association, May 2, 1927.

largely a mystery. Whipple[1] states in his review of the origin and significance of the constituents of the bile, "If our ignorance about the complete story of the bile pigments is disturbing, then our lack of understanding as to the source and internal metabolism of the bile acids is pathetic—this in spite of much careful study and investigation." The application of Van Slyke's gasometric method to the determination of bile acids in small amounts of dogs' bile, by Foster and Hooper[2] and Schmidt and Dart,[3] has made possible the accumulation of valuable data concerning the excretion of bile acids in the bile. Brakefield and Schmidt[4] have further devised a method for bile acid analysis in urine.

A fact established early in the history of bile physiology was the "circulation of the bile acids." There is no evidence, however, for a circulation of the bile pigments. The pigments, apparently, fulfill no useful function and are true waste products. Bile acids are rapidly absorbed from the intestinal contents and reappear in the bile. Foster, Hooper and Whipple,[5] in their bile fistula dogs, have noted that when moderate amounts of bile (about 1.8 gm. taurocholic acid) are given by mouth, about 90 per cent of the contained taurocholic acid is excreted during the first four hours; but when large doses (8 to 11 gm. of taurocholic acid) are administered the cholagogue effect is prolonged for many hours or days. Taurin administered intravenously has no effect on taurocholic acid excretion, but taurin and cholic acid fed by mouth increase the volume of bile and the taurocholic acid output. Further, these authors have observed a uniform excretion of taurocholic acid in the bile fistula dog during fasting periods. If these dogs receive a sugar diet during such periods there is a uniform and slightly lower excretion of taurocholic acid. This fall in taurocholic acid excretion appears analogous to the decrease in urinary nitrogen under similar conditions. Apparently there is an important endogenous factor in bile acid metabolism which may also be concerned with body protein metabolism. A meat-protein diet gives the highest output of bile acids for a six-hour period, but a high protein fed to a dog after a prolonged fast does not produce the expected rise in taurocholic acid excretion. Evidently, there is a diversion of some of the precursors of the bile acids to serve other purposes in the body. These observations indicate the existence of an exogenous factor influencing bile acid excretion, apparently related to the food proteins.

The bile acids, taurocholic and glycocholic acids can be readily split into their constituent groups:

Taurocholic acid = taurin + cholic acid.
Glycocholic acid = glycocoll + cholic acid.

Taurin is probably derived from the sulphur containing amino acids, cystin or cystein, of the food or body protein. Glycocoll may be synthesized in the body. The body contains, on the average diet, enough taurin and glycocoll for the production of bile acids

in any amount required, but the cholic acid is recognized to be the limiting factor in bile acid synthesis. Little is known concerning the structure of cholic acid, and nothing about its origin in the body. Since cholesterol has been suggested as the precursor of cholic acid, and hence a determining factor in bile acid synthesis, a review of cholesterol metabolism in human pathology would be of interest.

During the past three years we have made an intensive study of the cholesterol of the blood in various types of jaundice and diseases of the hematopoietic system. In this investigation 250 cases have been observed. Our findings add nothing new to the observations reported in the literature, but we believe our results warrant publication since they represent a comprehensive study of this phase of the jaundice problem. The method of Myers and Wardell[6] has been employed throughout under uniform conditions. For a standard we have utilized a solution of cholesterol in chloroform, standardized by the digitonin method. With this method, Myers[7] reports the cholesterol of normal whole blood to vary between 140 and 160 mg. per 100 cc. In our cases of obstructive jaundice the cholesterol was found to vary from 154 to 952 mg. per 100 cc. The increase was seen in the fraction of free cholesterol, the form in which it is present in the bile. Although no determinations of cholesterol in the bile have been made, it is reasonable to conclude that the rise in blood cholesterol was due to a retention. In obstructive jaundice the changes in blood cholesterol did not parallel variations either of the bilirubin or of the bile acids of the blood. In a case of great interest in this connection, a complete biliary obstruction followed the severance of the common bile duct and ligation of the stumps during a cholecystectomy. This patient was admitted to the hospital markedly jaundiced, with a cholesterol of 952 mg. per 100 cc. Two weeks after a repair of the common duct over a rubber tube, the cholesterol was 545 mg., and three months later, when the jaundice was not clinically visible, the cholesterol had diminished to 182 mg. per 100 cc. A subsequent blocking of the drainage tube resulted in a return of the jaundice with a rise in the blood cholesterol to 643 mg. per 100 cc. This increase in blood cholesterol is found in all types of obstructive jaundice, whether the obstruction be due to gall stones, malignancy or other mechanical causes. With improvement in the jaundice, the cholesterol lags behind the bilirubin in its return to normal. In cholecystitis and cholelithiasis no change was noted in the blood cholesterol unless there was an associated biliary obstruction. In phosphorus poisoning, occurring in human subjects and experimentally produced in animals, in acute yellow atrophy of the liver, cirrhosis of the liver and catarrhal jaundice, no variation from the normal has been observed in the blood cholesterol. We believe the determination of the cholesterol may be utilized practically as an aid in the differential diagnosis of these latter types of jaundice from obstructive jaundice. In hemo-

lytic anemias and primary anemias the blood cholesterol is markedly decreased. Our figures have ranged from 110 to 60 mg. per 100 cc. This decrease was found to be independent of the fall in the erythrocyte content of the blood. In animals in which an acute, severe anemia was produced experimentally there was observed an initial fall in the blood cholesterol, followed by a rise. The subsequent rise was observed at about the time the erythrocytes showed a return toward the normal count.

Although some similarity is evident in the structural formulas for cholesterol and cholic acid, and some experiments have been reported indicating a close biological relationship between these two compounds, Foster, Hooper and Whipple[8] have shown that cholesterol fed alone or with taurin causes no change in the excretion of bile acids. Beth[9] believes that in the assumption that cholic acid is formed from the disintegration of cholesterol, we have an explanation of the mechanism of the removal of cholesterol from the body in the elimination of bile acids in the bile, or, in pathologic conditions, in the urine. Comparative observations upon the changes in cholesterol and bile acids in normal and pathologic bloods are not sufficient to prove or disprove such a theory. However, there is no apparent relation between variations in the cholesterol of blood and the bile acids in cases studied by us.

Despite the large volume of data obtained on experimental animals, very little is known concerning the bile acid metabolism in human subjects. The great obstacle to the study of bile acid metabolism in human physiology and pathology has been the lack of an accurate and fairly rapid method for bile acid determination in the human blood. However, P. Szilard[10] has recently described a comparatively simple colorimetric method for the estimation of the bile acids of blood plasma or serum. With this technique bile acids may be determined in from 3 to 5 cc. of serum. It has been our experience that, within the limits of experimental error, this method yields a quantitative recovery of taurocholic or glycocholic acids when their concentration lies between 10 and 100 mg. per 100 cc. Best results are obtained by employing sufficient volume of plasma or serum so that there will be about 1 mg. of bile acids for the analysis.

Bile acids and bilirubin of the blood serum, and urobilin of the urine have been studied in a series of 100 cases, representing different types of jaundice. Shattuck, Preston and Browne,[11] and Shattuck, Preston and Killian[12] have found the icterus index of the blood serum the most dependable index of the hyperbilirubinemia, consequently in this investigation this procedure was utilized for the bilirubin of the blood. Elman and McMaster's[13] method has been employed for the urobilin excretion in the urine. The bile acids are reported in terms of milligrams of sodium glycocholate per 100 cc. of serum, and the urobilin as milligrams for the twenty-four-hour excretion of urine.

Discussion of Results. In Table I are presented the findings for 4 normal individuals and 11 miscellaneous cases. The normals were not jaundiced, and had icterus indices varying from 4.7 to 6.8. The bile acids of the blood serum ranged from 7 to 8 mg. as sodium glycocholate per 100 cc. For all normal individuals studied, some of whom are not reported here, the maximum variations have been from 7 to 12 mg. per 100 cc. In the case of gastric (Case 7, B. K.) and duodenal (Case 5, M. P.) ulcer, high figures are obtained for the bile acids of the blood. In the case of the gastric ulcer this increase in serum bile acids is found with an icterus index only slightly above normal. However, in the instance of the duodenal ulcer the icterus index is 15, with a bile acid figure of 22 mg. per 100 cc. Nine days later the icterus index has decreased to 6.6 and the bile acids to 11.2. Similar changes in the icterus index and bile acids of the blood serum are seen in A. S. At the height of the fever, due to the lobar pneumonia, the bile acid concentration is markedly increased, with an icterus index upon the upper limit of the zone of latent jaundice. One week later, after the crisis, both figures have made a rapid return in the direction of normal.

In Table II are grouped 15 cases of cholecystitis, in all of whom the diagnosis has been confirmed by postoperative examination of the tissue. Of these 3 only were jaundiced, giving figures for the icterus index above the zone of latent jaundice. Figures for urobilin excretion have not been reported in this group because, in our experience, single observations of the urobilin of the urine are of little value. These 3 cases gave evidence of biliary obstruction. In the remaining instances the icterus index varied from 4.7 to 12. It is very significant that in all of these patients there is seen a distinct increase in the concentration of bile acids in the blood serum without any relation to the bilirubin content of the serum. The concentration of bile acids is greater in some of the cases with normal icterus indices than in those with hyperbilirubinemias.

It is generally believed that the bile acids are produced in the liver, although the evidence to support this view is far from being complete. Smyth and Whipple[14] have reported that chloroform in remarkably small doses, incapable of causing recognizable histologic liver injury or clinical reaction, can effect a decrease in bile salts concentration in fistula bile. In large doses phosphorus has also a depressant effect upon bile salt output in fistula bile. Moreover, Foster, Hooper and Whipple[15] have observed a diminished excretion of bile from an Eck fistula liver. These authors conclude that such observations present more evidence to substantiate the theory that the bile salts are produced by the liver and not elsewhere in the body. However, it is equally logical to attribute the diminished excretion of the bile acids in the bile to a retention by the liver.

TABLE I.—NORMAL AND MISCELLANEOUS CASES.

Patient.	Sex.	Age.	Date.	Icterus Index.	Van den Bergh.		Bile acids in serum, mg. per 100 cc.	Urobilin in urine, mg. per vol.	Clinical jaundice.	Liver enlargement.	Remarks.
					Direct.	Indirect.					
1. H. S.	M.	17	12/2	4.7	0	0	7.0	0	0	0	Normal
2. L. B.	F.	47	11/19	6.8	0	0	7.0	0	0	0	Normal
3. F. C.	M.	40	11/22	5.6	0	0	8.0	0	0	0	Normal
4. A. G.	F.	37	3/3	5.0	0	0	7.0	0	0	0	Normal
5. M. P.	F.	33	10/12	15.0	0	+	22.0	..	0	0	Duodenal ulcer
			10/21	6.6	..	..	11.2	..			
6. G. S.	F.	22	2/14	7.5	0	0	11.4	..	0	0	Typhoid fever
7. B. K.	M.	47	2/24	6.3	0	0	30.0	0	0	0	Gastric ulcer
8. A. S.	M.	24	1/17	15.0	+	++	68.0	..	+	0	Pneumonia, temperature 104° F.
			1/24	7.3	0	±	15.0	..	0	0	Normal temperature
9. N. V.	M.	18	1/17	7.5	0	+	8.0	..	0	0	Pneumonia after crisis
10. M. M.	F.	..	1/8	3.7	0	0	Trace	..	0	0	Secondary anemia
11. A. B.	M.	31	2/10	5.4	0	0	Trace	..	0	0	Secondary anemia
12. A. G.	F.	37	3/8	5.0	0	0	Trace	..	0	0	Secondary anemia
13. H. P.	M.	51	3/21	4.2	0	0	Trace	..	0	0	Secondary anemia
14. W. R.	M.	46	9/23	3.1	0	0	14.0	..	0	0	Carcinoma stomach
15. G. R.	M.	50	11/9	4.4	0	0	10.2	..	0	0	Carcinoma stomach

TABLE II.—CHOLECYSTITIS.

Patient.	Sex.	Age.	Date.	Icterus index.	Van den Bergh.		Bile acids in serum, mg. per 100 cc.	Clinical jaundice.	Liver enlargement.	Remarks.
					Direct.	Indirect.				
1. P. E.	F.	5	10/3	9.2	0	+	55.0	0	0	Acute cholecystitis
2. D. F.	M.	30	3/24	20.0	0	+	48.0	+	0	Chronic cholecystitis
3. L. D.	F.	49	3/28	5.8	0	0	40.6	0	0	Chronic cholecystitis
4. D. P.	F.	46	3/7	40.0	++	+++	40.0	++	++	Stone in common duct
			3/14	43.4	++	+++	43.2			
5. M. K.	F.	42	3/11	12.0	0	+	30.0	0	0	Chronic cholecystitis
6. J. S.	M.	61	1/17	21.4	++	+++	37.0	++	0	Chronic—with cholelithiasis
7. I. B.	F.	36	2/17	4.7	0	0	41.6	0	0	Chronic cholecystitis
8. T. H.	M.	49	11/11	5.7	0	0	53.2	0	0	Chronic cholecystitis
9. F. W.	M.	50	1/26	5.8	0	0	51.0	0	0	Chronic cholecystitis with cholelithiasis
10. M. C.	F.	47	11/1	5.7	0	0	53.4	0	0	Chronic cholecystitis with cholelithiasis
11. R. K.	F.	29	4/6	5.8	0	0	44.6	0	0	Chronic cholecystitis
12. M. C.	F.	60	10/8	7.8	0	±	43.2	0	0	Chronic cholecystitis
13. A. B.	M.	58	3/8	7.9	0	±	51.0	0	0	Chronic cholecystitis
14. S. M.	M.	30	3/21	5.6	0	0	30.0	0	0	Chronic cholecystitis
15. A. W.	M.	38	3/25	9.6	0	±	37.4	0	0	Chronic cholecystitis

TABLE III.—LIVER DISEASE.

Patient.	Sex.	Age.	Date.	Icterus index.	Van den Bergh.		Bile acids in serum, mg. per 100 cc.	Urobilin in urine, mg. per vol.	Clinical jaundice.	Liver enlargement.	Remarks.
					Direct.	Indirect.					
1. S. R.	F.	..	9/14	83.3	+++	+++	....	....	+++	++	Cirrhosis of liver
			9/21	50.0	+++	+++					
			9/27	62.0	+++	+++	38.4				Laparotomy and cholecystostomy
			9/30								
			10/3	29.9	++	++	35.0				
2. L. L.	M.	53	12/29	32.2	+++	+++	....	150			
			12/31	30.0	+++	+++	93.6	175	++	++	Cirrhosis of liver
			1/7	36.1	+++	+++	....	150			
			1/10	....	....	....	....	118			
			1/11	....	....	....	....	....	....	....	Laparotomy
3. F. K.	M.	58	1/5	7.1	0	0	52.0	....	....	....	Abdominal fluid
			1/13	17.6	....	....	....	60	+	++	Cirrhosis of liver
			1/25	9.4	0	+	68.0	77			
				4.0	0	0	28.4	....	....	....	Abdominal fluid
			2/5	9.0	0	+	....	61			
4. P. B.	M.	37	3/21	9.4	0	+	22.8	....	0	++	Echinococcus cyst of liver
5. S. L.	M.	28	1/8	4.2	0	0	50.0	....	0	++	Echinococcus cyst of liver
6. E. W.	F.	62	2/14	202.7	++++	++++	46.0	....	++++	....	Toxic hepatitis
				204.0	++++	++++	58.0	....	....	....	Liver small, lobules showing central necrosis; cause not determined
7. M. B.	M.	63	2/24	8.8	0	+	38.4	160	0	+	Banti's disease
8. M. C.	M.	55	1/11	16.6	+	+	53.5	470	+	....	Cirrhosis of liver
9. C. C.	M.	40	12/20	45.4	++++	++++	42.4	....	++	+	Pneumonia; acute hepatitis; died
10. H. L.	M.	49	4/29	25.0	+	++	....	148	....	....	Arsenical hepatitis (lues)
			5/2	....	....	....	....	36			
			5/4	....	....	....	....	Trace			
			5/8	15.0	0	+	32.0	Trace	+	+	

In Table III data are presented for 10 patients with liver disease representing varying degrees of hyperbilirubinemia, the icterus indices varying from 4.2 to 204. The urobilin output in the urine is also high in those cases in which it was determined. All of these patients present abnormally high figures for bile acids, ranging from 22.8 to 93.6 mg. per 100 cc. It is of interest to note that the changes in the concentration of bile acids in the blood bear no relation to variations in bilirubin. Smyth and Whipple found that the liver injury produced by liver poisons sometimes depressed, and at other times was without influence upon the excretion of bile pigments. Apparently, then whatever part the liver plays in bile salt metabolism may, in experiments and in pathologic conditions, be affected independently of its function in bile pigment metabolism. Moreover, it appears possible that the diminished excretion of bile salts in the bile after liver injury may be due to a retention and not to a diminished formation. In 2 instances (Case 2, L. L., and Case 3, F. K.) the bilirubin and bile salts have been determined in the ascitic fluid. A comparison of these figures for the abdominal fluid with the figures for the blood serum demonstrates that the bile salts pass more readily into other body fluids from the blood than does bilirubin. Experiments are under way at the present time to obtain more data on this question. If this proves to be a fact it may help to explain the lack of parallel changes in the bile acids and bilirubin of the blood in cases of marked jaundice such as seen in Case 6 (E. W.).

TABLE IV.—BILIRUBIN AND BILE ACIDS OF BLOOD OF RABBITS IN EXPERIMENTAL ANEMIAS AND LIVER INJURIES.

	Blood sugar, mg. per 100 cc.	Bile acids, mg. per 100 cc.	Icterus index.	
Control rabbits	..	6.4	1.9	Average for 6 rabbits
Rabbit 82	..	6.0	8.0	Acute hemolysis produced by Cl. Welchii—5 days
Rabbit 84	..	Trace	12.5	5 days
Rabbit 86	..	6.0	4.5	6 days
Rabbit 87	..	Trace	6.5	6 days
Rabbit 84	123	Trace	1.9	Control
	123	6.0	3.0	48 hours after 20 mg. P. per kilo
Rabbit 26	129	11.0	2.1	Control
	105	16.0	4.0	47 hours after 20 mg. P. per kilo
Rabbit 70	123	10.0	2.2	Control
	130	17.2	4.2	47 hours after 10 mg. P. per kilo
Rabbit 67	130	8.0	2.2	Control
	38	18.2	6.5	At time of death; 28 hours after 20 mg. P. per kilo

Table IV presents some of the experimental data on the influence of hemolysis and liver poisons upon the icterus index and bile acids

of the blood. In 6 control rabbits the average icterus index was 1.9 and the bile acids 6.4 mg. per 100 cc. An acute experimental anemia was produced by the intramuscular injection of whole broth cultures of Cl. Welchii. Detailed information of these experiments is given in a paper by Killian, Patterson and Kast.[16] Data for 4 of these rabbits are presented in the table at the height of the anemia. The icterus index varies from 4.5 to 12.5, but the bile acids are not increased. In fact, in 2 instances the bile acid content of the blood was so low that satisfactory quantitative determinations could not be made, and these are reported as traces. In the 4 following animals a liver injury was produced by the subcutaneous injection of phosphorus dissolved in almond oil, 10 to 20 mg. of phosphorus per kilogram of body weight. Phosphorus poisoning produces a marked reduction in blood sugar resulting in a hypoglycemia, causing the death of the animal in convulsions. The production of the hypoglycemia appears usually in the last twelve hours of a forty-eight-hour period, but the rapidity of its appearance depends upon the state of nutrition of the animal. In Rabbits 84, 26 and 70 the bloods were obtained before the appearance of the hypoglycemia, and in the last (67) at the time of death. In all of these rabbits there is seen a rise in both the icterus index and bile acids of the blood and this increase appears before any evidence of change in blood sugar. Liver injury with phosphorus, then, leads to an increase of both bile pigment and bile acids of the blood. The rise in icterus index is, however, not as great as seen in the acute anemias. Foster, Hooper and Whipple[17] also have noted that red blood cells fed by mouth, or hemolyzed and injected intravenously have no influence upon the level of bile acid excretion in the bile.

The findings for 9 cases of hemolytic anemias are tabulated in Table V. The case of congenital hemolytic icterus (P. B.) shows a gradually decreasing icterus index following the blood transfusions and splenectomy. The urobilin output in the urine increases temporarily and finally drops to a negative reaction. The bile acids remain persistently above normal, varying from 32 to 62 mg. per 100 cc. serum. In the 2 instances of splenomegaly following, bile acids of 28 and 30 mg. are found with icterus indices of 7.5 and 14.2 respectively. In the 6 patients with pernicious anemia widely different concentrations of bile acids, 11 and 36 mg. per 100 cc. are found with relatively identical icterus indices. One case of pernicious anemia (E. G.) presents interesting, but wholly unexpected, changes in bile acids of the blood with improvement in the blood picture on a high-protein (liver) diet. The first specimen of blood gives an icterus index of 11.5 with 19.6 mg. of bile acids per 100 cc. blood. At this time the output of urobilin in the urine amounted to 470 mg. for a twenty-four-hour period. After fifteen days of a high-protein (liver) diet the erythrocytes had increased from 1.5 to 2.7 millions per c.mm., and the hemoglobin rose from 42 to 68

TABLE V.—HEMOLYTIC ANEMIAS.

Patient.	Sex.	Age.	Date.	Icterus index.	Van den Bergh.		Bile acids in serum, mg. per 100 cc.	Urobilin in urine, mg. 24 hrs.	Remarks.
					Direct.	Indirect.			
1. P. B.	F.	3 8/12	12/21/26	....	....	....	....	....	Congenital hemolytic icterus
			12/22	17.6	0	+	46.6	24	Splenomegaly
			12/29	19.0	0	+	36.0	40	Increased fragility of red blood cells
			12/30	17.5	0	+	49.0	14	
			12/31	....	....	....	....	....	Transfusion—360 cc.
			1/6	15.3	0	+	62.0	106	Fe = 34.8 mg. Hb = 9.9 gm.
			1/7	....	....	....	....	70	Transfusions and splenectomy
			1/11	10.7					
			1/17	6.4	0	±	32.0	0	
			2/1	5.4	0	−	36.4	0	Fragility normal
2. M. M.	F.	1 3/12	12/27/26	14.2	0	+	30.0	....	Splenomegaly; undetermined type
3. D. A.	F.	5 11/12	2/18	7.5	0	±	28.0	125	Purpura hemorrhagica: splenomegaly; Fe = 20.8 mg. Hb = 5.2 gm. per 100 cc.
			2/25	....	....	....	....	....	Splenectomy
4. E. K.	M.	44	3/24	7.5	0	±	11.0	....	Pernicious anemia
5. W. B.	M.	51	3/18	8.0	0	+	31.0	....	Pernicious anemia
6. E. G.	..	..	11/9	....	....	....	....	....	Pernicious anemia
			11/11	11.5	0	+	19.6	470	Hb = 42%; R. B. C. = 1.5 m. per c.mm.; liver diet begun 11/11
			11/26	6.2	0	±	36.0	0	Hb = 68%; R. B. C. = 2.7 m. per c.mm.
7. M. B.	F.	55	4/22	11.1	0	±	28.0	....	Pernicious anemia
			4/22	....	....	....	....	....	R. B. C. = 1.14 m. per c.mm.; liver diet begun 4/22
			4/29	....	....	....	....	62	
			5/1	....	....	....	....	Trace	
			5/3	....	....	....	....	69	
			5/11	5.1	0	0	30.0		
8. H. S.	F.	51	4/27	10.0	0	+	32.5	....	Pernicious anemia; R. B. C. = 1.92 m. per c.mm.; liver diet begun 4/27
			5/9	5.0	0	0	35.2		
			5/18	21.4	0	+	33.2	....	
9. F. B.	M.	43	4/29	10.3	0	+	26.8	....	Pernicious anemia; Hb = 29%; R. B. C. = 1.204 m. per c.mm.
			5/6	13.0	0	+	24.0	....	Liver diet begun 5/6
			5/15	8.4	0	+	26.0		5/17—Hb = 38%; R. B. C. = 1.210 m. per c.mm.
			5/24	9.3	0	±	25.0	....	

TABLE VI.—CATARRHAL JAUNDICE.

Patient.	Sex.	Age.	Date.	Icterus index.	Van den Bergh.		Bile acids in serum, mg. per 100 cc.	Cholesterol.	Urobilin in urine, mg. per 24 hrs.	Clinical jaundice.	Remarks.
					Direct.	Indirect.					
1. B. P.	M.	21	12/22	40.0	+++	+++	46.6	0.096	920	++	Gave history of clay-colored stools
			12/25	....	....	....	....	....	270		
			12/30	20.6	++	++	32.0	....	330		
			1/1	....	....	....	....	....	164		
			1/4	38.9	++	++	50.0	....	280		
			1/5	....	....	....	....	....	650		
			1/8	....	....	....	....	....	....	+++	History of clay-colored stools
2. D. R.	M.	20	10/7	100.0	++	+++	....	....	183		
			10/9	....	....	....	....	....	994		
			10/10	....	....	....	....	....	0		
			10/11	....	....	....	....	....	470		
			10/12	....	....	....	....	....	0		
			10/13	176.4	++++	++++	216.0	....	0		
			10/18	166.6	++++	++++	210.0	....	0		
			10/20	....	....	....	....	....	....	....	Cholecystogastrostomy
			10/27	101.4	++++	++++	178.0	....	115		
3. A. M.	M.	29	11/3	65.2	++	+++	86.0	....	1090		
			1/7	66.6	+++	+++	....	....	0	++	
			1/11	78.8	++++	++++	46.0	....	1380		
			1/12	....	....	....	....	....	1990		
			1/13	....	....	....	....	....	850		
			1/14	....	....	....	....	....	94		
4. A. K.	M.	31	1/18	37.5	++	+++	56.2	....	0	+++	
			4/19	93.8	++++	++++	32.0	....	1350		
			4/25	42.9	++	++	45.6	....			

TABLE VII.—OBSTRUCTIVE JAUNDICE.

Patient.	Sex.	Age.	Date.	Icterus index.	Van den Bergh.		Bile acids in serum, mg. per 100 cc.	Urobilin in urine, mg. per vol.	Clinical jaundice.	Liver enlargement.	Remarks.
					Direct.	Indirect.					
1. J. M.	M.	67	3/18	66.4	+++	++++	37.0	6	++++	++	Carcinoma of head of pancreas
			3/21	96.1	++++	++++	45.2	23	....	....	No bile in feces
			3/28	120.0	++++	++++	70.8	0			
			3/30	176.4	++++	++++	65.0	0	....	....	Cholecystogastrostomy
			3/31	136.3	++++	++++	50.0	60			
2. M. S.	M.	55	11/19	37.0	+++	+++	23.2	115	+++	++	Chronic pancreatitis and acute cholangitis
			11/28	37.0	....	....	....	0			
			12/15	....	....	....	....	....	....	....	Cholecystoduodenostomy
			3/19	5.0	....	....	22.8	0			
3. S. S.	M.	64	10/19	150.0	++++	++++	34.4	60	++++	++	Carcinoma — origin undetermined
			3/18	206.8	++++	++++	32.0	0	++++	++	metastases to liver; autopsy
4. C. C.	M.	51	4/6	126.0	++++	++++	78.2	0	+++	++	Carcinoma of stomach; metastases
			4/8	250.0	++++	++++	72.0	0	+++	++	to liver
5. L. C.	M.	3 m.	4/4	120.0	++++	++++	25.0	0	+++	....	Congenital absence of bile ducts
6. M. G.	F.	59	3/12	157.8	++++	++++	34.0	0	+++	++	Carcinoma of gastrointestinal tract;
			3/21	126.3	++++	++++	32.0	0			metastases to liver; operation
7. M. T.	....	....	9/14	31.2	+	++	....	80	++	0	Chronic cholecystitis, stone in common duct
			9/16	....	....	....	....	....	....	....	Operation
			9/21	23.2	+	++	....	40			
			10/7	19.2	0	++	99.0	0			
8. E. C.	F.	29	2/3/26	44.0	++	++	....	378	++	....	4 mos. after repair of stricture of common duct
			6/5/26	11.5	....	+	....	470	0		
			6/6	....	....	....	....	235			
			6/7	....	....	....	....	235			
			6/8	....	....	....	....	624			
			6/9	....	....	....	....	120			
			6/10	....	....	....	....	470			
			6/11	18.0	....	+	....	470	....	....	Division of stricture; insertion of tube
			3/21/27	16.6	....	+	34.0	480			
			3/30	23.0	±	+	35.0	230	....	....	Phenoltetrachlorphthalein excretion: 15 min. = 20%; 60 min. = 10%
			4/12	18.7	0	+	32.8	450			

per cent. The icterus index had diminished to 6.2, and no urobilin was found in the urine. However, his bile acids had increased to 36 mg. per 100 cc. The reason for this increase in bile acids after improvement in the anemia is obscure. It may, however, find an explanation in the observations of Foster, Hooper and Whipple upon the influence of the diet upon the excretion of bile salts in bile fistula dogs. These authors have stressed the importance of an exogenous as well as an endogenous factor influencing bile acid formation. It is possible that the high-protein diet has rendered available to the body more of the precursors from which bile acids are prepared. The influence of a high-protein (liver) diet upon bile pigment and bile acid metabolism is under investigation at the present time, and the results will be presented in a future communication.

Four cases of catarrhal jaundice have been studied, and the data obtained are presented in Table VI. Two of these cases before admission to the hospital gave histories of "clay-colored" stools. Marked variations are noted in the urobilin excretion, in some instances (Cases 2, 3 and 4) ranging from a negative reaction to over 1 gm. in twenty-four hours. In the cases of catarrhal jaundice reported by Klemperer, Killian and Heyd,[18, 19] there are presented clinical and histologic evidence of biliary obstruction in the bile capillaries of the liver. Wallace and Diamond[20] have reported, in catarrhal jaundice, marked fluctuations in urobilin excretion, the curve showing peaks of large amounts and dropping off to a scanty excretion or a negative reaction within twenty-four hours, with a prompt subsequent rise. However, the urobilin never remains permanently absent from the urine in catarrhal jaundice. Charts I, II and III present graphically the variations in the icterus index of the blood and of the urobilin of the urine in 3 cases of catarrhal jaundice. It is evident from the graphs that the urobilin output in the urine does not run parallel with the changes in the bilirubin of the blood serum. Moreover, great variations are observed in urobilin excretion from day to day. For the first four days of observation no urobilin was found in the urine of A. M. (Chart III), but within forty-eight hours the output of urobilin rose to 1990 mg., for twenty-four hours, and during the subsequent twenty-four hours only 850 mg. were excreted. D. R. (Chart II) gave negative reactions for urobilin for forty-eight hours on two occasions, and no urobilin was found in the urine of B. P. for one period of twenty-four hours. If the excretion of urobilin in the urine is to be utilized as an aid in the differential diagnosis between obstructive and catarrhal jaundice, the determinations of urobilin in the urine must be continued over a period of not less than five days. A hyperbilirubinemia is seen in all cases, and an increase in the bile acids of the blood. However, the bile acids in Cases 1, 3 and 4 do not show a decrease paralleling the drop in icterus index, but, on the

contrary, a slight increase is noted. Case 2 gives unusually high figures for blood bile acids reaching the maximum at 210 mg. per 100 cc. This patient showed a rising icterus index and an absence of urobilin from the urine for five days. He was operated upon on the suspicion of a mechanical obstruction. Although at operation no obstruction was found, a cholecystogastrostomy was done and following this the icterus index continuously decreased, the urobilin output in the urine rose. A diminution of the blood bile acids also followed the cholecystogastrostomy.

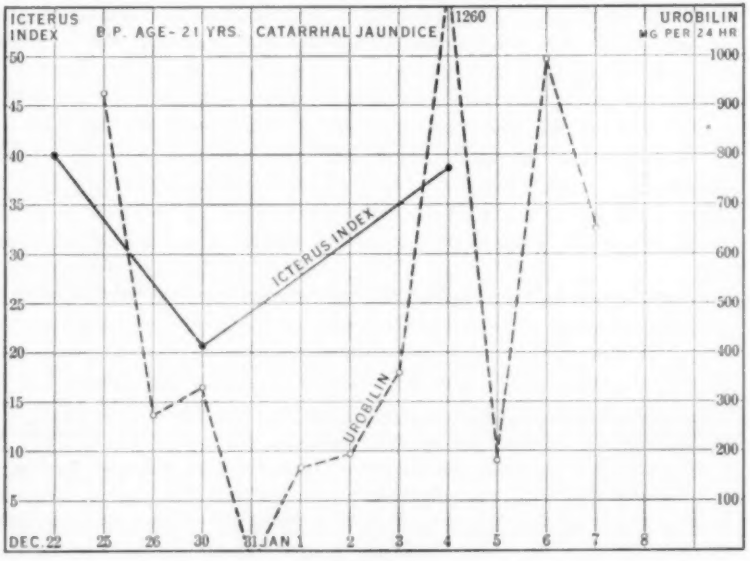


CHART I

In obstructive jaundice the hyperbilirubinemia is indicated by a marked elevation of the icterus index of the blood serum. Urobilin is negative or excreted in minute amounts. When the obstruction is relieved, as in Case 1, urobilin reappears in the urine. This patient died about twenty-four hours after operation from a perforated duodenal ulcer. The bile acids of the blood are increased above normal, but this increase does not parallel the rise in icterus index. In Case 1 (carcinoma of the head of the pancreas) there is evident a rapid accumulation of both bile pigment and bile acids in the blood serum. The bile acids reach their maximum concentration at 70.8 mg. per 100 cc., when the icterus index had risen to 120. During the following two days the icterus index mounts to 176.4, but the bile acids decreased to 65 mg., and on the last day the bile acids are but 50 mg. per 100 cc., with an icterus index of 136.3. In Cases 3 and 4 again a slight decrease is noted in blood

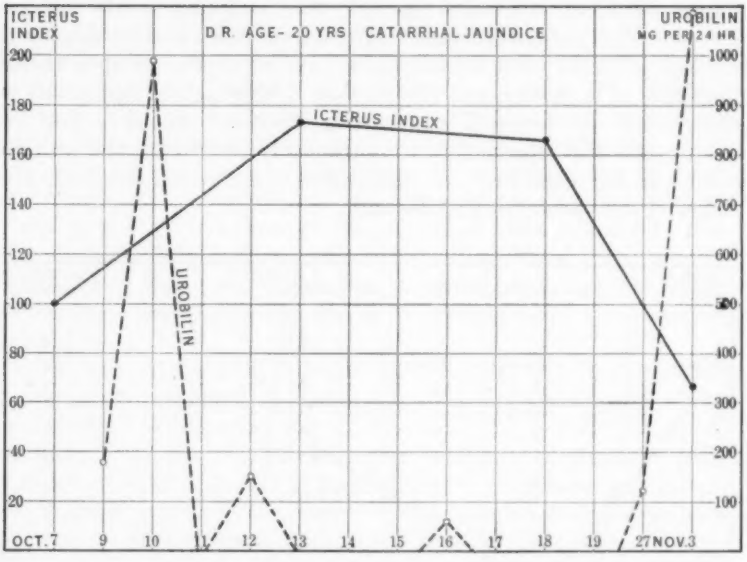


CHART II

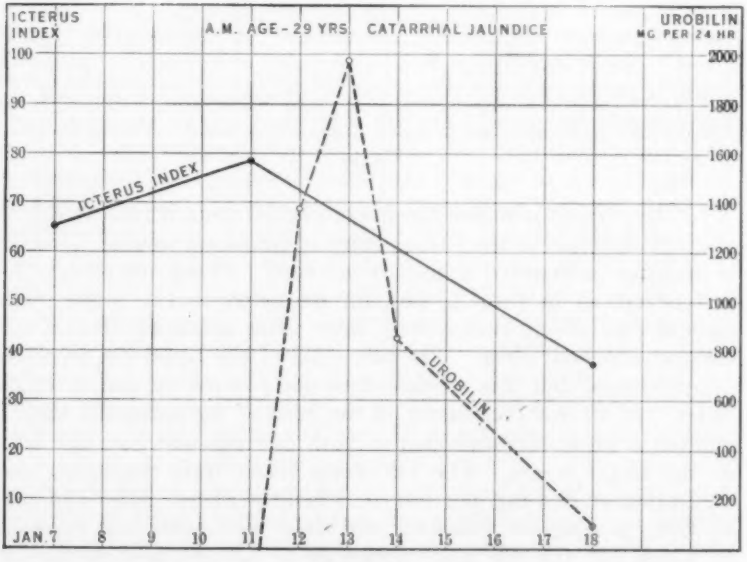


CHART III

bile acids, although the icterus index is seen to increase. Moreover, in Cases 5 and 6, in obstructions of long standing, the icterus indices are from twenty to thirty times the normal figures, but the bile acid concentration is but three to four times the controls. Brakefield and Schmidt produced obstructive jaundice in dogs by ligation and subsequent resection of the common bile duct. They noted that the production of the jaundice was followed by a urinary excretion of bile acid and bile pigment, but the output of bile acid decreased with time and finally became a very small quantity. An injection of taurocholic acid led to an increased excretion of this substance. Moreover, it was found that the ability of the jaundiced dog to detoxicate benzoic acid was markedly diminished after the onset of the jaundice, and microscopic sections of the livers showed extensive morphologic changes. According to the observations of these authors, the diminished excretion of the bile acids was due to an impairment of the liver's ability to produce the acids. In our results the comparatively low bile acids of the blood in obstructive jaundice of long standing may be due to a similar cause. However, there is another possible explanation. Bile acids, as their salts, may penetrate body tissues or body fluids other than the blood more readily than does bilirubin.

Cases 2 and 7 demonstrate that following relief of the obstruction by surgery, the bile acids do not show a decrease corresponding to the improvement in the hyperbilirubinemia. In Case 8 it is evident from the slight but persistent elevation of the icterus index the excretion of urobilin and the retention of phenoltetrachlorphthalein in the blood serum that a permanent damage to liver drainage has probably resulted from injury to the biliary system. There is both laboratory and clinical evidence in this case of a chronic partial biliary obstruction. The figures for bile acids, about three to four times the normal, do not reach the high level seen in the rapidly progressing jaundice of Case 1.

Summary. The cholesterol of whole blood was found to be increased in obstructive jaundice. In catarrhal jaundice, phosphorus poisoning, acute yellow atrophy of the liver and cirrhosis of the liver, no change in blood cholesterol was noted. In hemolytic anemias a decrease in blood cholesterol was observed, with a rise toward normal when the erythrocyte volume of the blood increased. In hemolytic anemias the changes in blood cholesterol were independent of variation in the red cell count.

With Szilard's method the bile acids of normal human blood varied from 7 to 12 mg. per 100 cc. of serum, determined as sodium glycocholate.

In cholecystitis an increase of the bile acids of the blood to from four to seven times the normal figure was noted. This increase in bile acids was found to be independent of any similar changes in the bilirubin of the blood serum.

In diseases of the liver, including cirrhosis of the liver, echinococcus cyst of the liver, hepatitis associated with pneumonia, and in catarrhal jaundice, the elevation of the bile acids was less than the accumulation of bilirubin in the blood serum, whereas in other cases the rise in bile acids greatly exceeded the increase in bilirubin of the blood serum. This chemical evidence supports the observations of Smyth and Whipple upon the effects of liver injury upon bile acid and bile pigment excretion in the bile. Comparison of the distribution of bilirubin and bile acids between the blood serum and abdominal fluid suggests that the bile salts may pass more readily into other body fluids or tissues than does bilirubin. The failure of the damaged liver to excrete bile acids may be due to a retention rather than to a decreased formation.

Animal experiments demonstrate that an acute hemolysis will increase the bilirubin of the blood serum, but does not influence the concentration of bile acids. Phosphorus poisoning, however, produces both a hyperbilirubinemia and an increase in the bile acids of the blood. The increase in bile acids observed after phosphorus poisoning apparently is due to a retention.

Splenectomy or a high-protein (liver) diet were observed to diminish the bilirubin content of the blood serum and the urobilin excretion in the urine in hemolytic anemias. However, the bile acids do not show a parallel decrease. In one case of pernicious anemia the high-protein (liver) diet produced an increase in the bile acids of the blood, an effect probably analogous to the influence of high-protein diet on bile acid production observed in animals.

In catarrhal jaundice, it was again seen that the decrease in the bilirubin of the blood serum observed during the subsidence of the jaundice was not accompanied by a parallel fall in the bile acids of the blood. Observations upon cases of catarrhal jaundice demonstrate the great practical value of determinations of the urobilin of the urine as an aid in the differential diagnosis between catarrhal and obstructive jaundice.

Acute obstructive jaundice produced a rapid rise in the bilirubin of the blood serum and a marked increase in bile acids, to about ten times the normal figure. In chronic obstructions, however, the bile acid increase in the blood is much less, to but three to four times the normal. This smaller concentration of bile acids in the blood in chronic obstructions may be attributed to impairment of the liver's ability to produce bile acids after long obstructions, as observed by Brakefield and Schmidt. On the other hand, it may also be due to a more rapid penetration of the bile salts than of the bile pigment into other body fluids or tissues.

REFERENCES.

1. Whipple, G. H.: Phys. Rev., 1922, **2**, 440.
2. Foster, M. G., and Hooper, C. W.: J. Biol. Chem., 1919, **37**, 335.
3. Schmidt, C. L. A., and Dart, A. E.: J. Biol. Chem., 1920–1921, **45**, 415.
4. Brakefield, J. L., and Schmidt, C. L. A.: J. Biol. Chem., 1926, **67**, 523.
5. Foster, M. G., Hooper, C. W., and Whipple, G. H.: J. Biol. Chem., 1919, **38**, 379.
6. Myers, V. C., and Wardell, E. L.: J. Biol. Chem., 1918, **36**, 147.
7. Myers, V. C.: J. Lab. and Clin. Med., 1920, **5**, 776.
8. Foster, M. G., Hooper, C. W., and Whipple, G. H.: J. Biol. Chem., 1919, **38**, 421.
9. Beth, H.: Wien. Arch. f. inn. Med., 1921, **2**, 563.
10. Szilard, P.: Biochem. Ztschr., 1926, **173**, 440.
11. Shattuck, H., Preston, M., and Browne, J. C.: Am. J. Med. Sci., 1925, **170**, 510.
12. Shattuck, H., Preston, M., and Killian, J. A.: J. Lab. and Clin. Med., 1927, **12**, 802.
13. Elman, R., and McMaster, P. D.: J. Exp. Med., 1925, **41**, 503.
14. Smyth, F. S., and Whipple, G. H.: J. Biol. Chem., 1924, **59**, 623.
15. Foster, M. G., Hooper, C. W., and Whipple, G. H.: J. Biol. Chem., 1919, **38**, 393.
16. Killian, J. A., Patterson, M., and Kast, L.: Arch. Int. Med. (in press).
17. Foster, M. G., Hooper, C. W., and Whipple, G. H.: J. Biol. Chem., 1919, **38**, 421.
18. Klemperer, P., Killian, J. A., and Heyd, C. G.: Arch. Path. and Lab. Med., 1926, **2**, 631.
19. Heyd, C. G., Killian, J. A., and Klemperer, P.: Surg., Gynec. and Obst., 1927, **44**, 489.
20. Wallace, G. B., and Diamond, J. S.: Arch. Int. Med., 1295, **35**, 698.

REVIEWS.

ROENTGEN RAYS AND RADIUM IN THE TREATMENT OF DISEASES OF THE SKIN. By GEORGE M. MACKEE, M.D., Professor of and Director of the Department of Dermatology and Syphilology, New York Post-Graduate Medical School and Hospital. Second edition. Pp. 788; 354 engravings and 31 charts. Philadelphia: Lea & Febiger, 1927. Price, $10.00.

THIS work, the long-awaited second edition of a book which it is not too much to say is the standard manual of the world on the application of Roentgen ray and radium to cutaneous disease, is in every particular an improvement even on its distinguished predecessor. The basic physical considerations underlying the use of radiotherapeutic agents are presented in some 65 pages. Apparatus receives the most careful and detailed consideration. It is possible for the conscientious student to ground himself from this book in the thorough knowledge of his instrument, which is essential to the best results. New material dealing with the recent developments in the accurate measurement of Roentgen ray dosage had had elaborate consideration and of necessity some matter, largely of historical value, has been relegated to the background. To the average practising dermatologist some of the mathematical presentations, particularly those dealing with wave-length measurement, in which the author has had the collaboration of Professor Kovarik, of Yale, will be impossible of comprehension but will be important to the investigator. The use of a kilovolt basis for the estimation of indirect unfiltered dosage instead of spark gap is a step in the direction of increased exactitude. The histopathology and clinical manifestations of Roentgen ray and radium effect, the influence of overdosage and of ultraviolet light, the unfavorable by-effects and the means of avoiding them, are so thoroughly dealt with that even the tyro must approach the field with respect and caution.

Of the technical sections dealing with treatment methods, the simple statement that a beginner can actually proceed to the safe use of the Roentgen ray in cutaneous medicine on the basis of the matter presented, is the highest possible praise. The latter sections of the book deal with individual disease conditions of the skin in which radiotherapy is of value. There are penetrating summaries of causes of failure. Over and over again, the reader is

cautioned in regard to the avoiding of trouble in the most unmistakable and definite terms. There are valuable bibliographic summaries attached to various chapters and a section on the medico-legal relations of Roentgen and radium therapy which combines a world of wisdom with an extensive review of the law. The appendix deals with the recent work done by Bucky and other investigators on the Müller long-wave-length tube.

Only two suggestions occur to the reviewer: First, that as rapidly as they can be collected the long-range efficiency of radiotherapeutic methods in the inflammatory dermatoses especially should be collected. The problem of relapse in acne, eczema and so forth, and the systemic effect of irradiation upon blood chemistry and the functions of the body, needs better representation in the literature and in textbooks. A minor suggestion would include the abandoning of the terminology "intensive," "subintensive" and so forth, and the substitution throughout the work of dosage expressed in the standard MacKee skin unit, which is now the practically universal terminology of American dermatologic radiotherapy.

Such a work as this may well be looked upon as an enviable accomplishment, the precious fruit of a long and active life as an investigator and clinician. MacKee's efforts have literally transformed the field of cutaneous radiotherapy from a terrain of occultism and confusion to a domain of order and practical standardization. It goes without saying that his book is an absolutely indispensable adjunct to the work of every dermatologist and radiotherapist—a text unique in its completeness, originality and serviceability.

J. S.

A MANUAL OF MATERIA MEDICA AND PHARMACOLOGY. Especially designed for Students of Pharmacy and Medicine, as well as for Druggists, Pharmacists and Physicians. By DAVID M. R. CULBRETH, PH.G., M.D., Professor-Emeritus of Botany, Materia Medica, and Pharmacognosy in the Maryland College of Pharmacy, Department of the University of Maryland, Baltimore, Md. Pp. 1001; 497 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $8.00.

THIS is a new edition (seventh) corresponding with the tenth revision of the U. S. Pharmacopœia and the fifth revision of the National Formulary. It is primarily a concise and authoritative treatise on pharmacognosy and drug chemistry. The author uses the word pharmacology as "a similar but more modern term" for materia medica; his discussion of drug actions savors more of empiricism than of modern pharmacodynamics. The book will be useful to the student or practitioner of pharmacy rather than to the medical student or physician.

C. S.

HYGIENE AND SANITATION FOR NURSES. By GEORGE M. PRICE, M.D., Director of the Union Health Center, New York City. Fifth edition. Pp. 286. Philadelphia: Lea & Febiger, 1927. Price, $2.25.

NEW discoveries in the field of hygiene, as well as in the methods of dealing with certain aspects of public health work, have made necessary this new edition of a well-known textbook for nurses. It treats such topics as Hygiene, Sanitation and Public Health Nursing, Hygiene of Habitations, Hygiene of Foods and Food Supply, Hygiene of Childhood, Hygiene of Occupations, Infectious Diseases and their Prevention, Constitutional Diseases and Personal Hygiene. It is a useful book for both graduate and student nurses.

S. G.

SURGERY: PRINCIPLES AND PRACTICE. By ASTLEY PASTON COOPER ASHHURST, A.B., M.D., F.A.C.A. Third edition. Pp. 1179; 1046 illustrations; 15 colored plates. Philadelphia: Lea & Febiger, 1927. Price, $10.00.

THIS, the third edition of this work, brings the subject matter of the principles and practice of surgery up to date. The author endeavors to teach his readers to know, feeling that they must learn later to do. He, therefore, emphasizes the principles of surgical pathology, diagnosis, indications for and methods of treatment. Many of the more important operations are described in detail and at least one well-recognized operation in each incidence is given. One of the pleasing features is the proportionate space and attention given to various subjects. In other words, the more important and usual diseases are given the greatest attention. This edition has added new material or reconstructed the old text on special subjects as alkalosis, tularemia, septicemia, granuloma inguinale, local anesthesia, pulmonary tuberculosis, massive collapse of the lung and many others. As a practical reference book for students and practitioners the work cannot be surpassed.

E. E.

A TEXTBOOK OF PATHOLOGY. By ALFRED STENGEL, Professor of Medicine, University of Pennsylvania; and HERBERT FOX, Professor of Comparative Pathology, University of Pennsylvania, and Pathologist to the Philadelphia Zoölogical Garden. Eighth edition; reset. Pp. 1138; 552 illustrations and 18 colored plates. Philadelphia: W. B. Saunders, 1927. Price, $10.00.

THIS work, designed as a textbook, is arranged in concise paragraphic form. Thus each subject is discussed under headings, as

Definition, Etiology, etc. Part I (447 pages) is devoted to General Pathology and Part II (691 pages) to Special Pathology. References to literature are used very sparingly. The illustrations are well chosen. Some important subjects are treated very briefly, but one remembers this is a one-volume treatise. Appropriate discussions of sickle-cell anemia, tularemia, scarlet fever, and so forth, indicate this work is not behind on recent developments. The subject matter throughout is fully commensurate with the dimensions of the volume. V. M.

NORMAL MIDWIFERY FOR MIDWIVES AND NURSES. By G. W. THEOBALD, Professor of Obstetrics and Gynecology in the Chulalankarana University, Bangkok. Pp. 258; 28 illustrations. New York: Oxford University Press, American Branch, 1927.

GRADUATE nurses in England usually qualify after graduation as midwives. As the title indicates, this book is intended for this group. It, therefore, discusses the subject of Obstetrics in a manner somewhat different from the textbooks written for nurses in this country. It takes for granted that most of the deliveries are to take place in a home and it is most fertile in its suggestions of how to utilize ordinary household equipment at such times. The material was originally given as a series of lectures to midwives and the book retains much of the conversational style. The language is direct and impelling and essential points are always summed up. The author has a delightful sense of humor. Most of the illustrations are original. S. G.

A TEXTBOOK OF PHYSIOLOGY. By WILLIAM H. HOWELL, PH.D., M.D., SC.D., LL.D., Professor of Physiology, School of Hygiene and Public Health, Johns Hopkins University. Tenth edition. Pp. 1081; 308 illustrations. Philadelphia: W. B. Saunders Company, 1927.

THE customary triennial revision of this standard and deservedly popular book. As noted in the author's preface, it is utterly impossible for any one worker to be thoroughly familiar with the present status of all phases of such a vast topic, so that one need not be surprised if the latest developments in one's pet subject are not always to be found. The advanced student will be helped by the numerous foot-note references, and here too it is perhaps asking too much that more recent authorities should always be quoted. The book's good points are too well known to need further emphasis—we still regard it as the best on the subject for the "undergraduate" medical student. E. K.

BONE SARCOMA: THE PRIMARY MALIGNANT TUMORS OF BONE AND THE GIANT-CELL TUMOR. By ANATOLE KOLODNY, PH.D., M.D. Pp. 214; 104 illustrations. Chicago: The Surgical Publishing Company of Chicago, 1927. Price, $5.00.

A CAREFUL digest of the 700 cases collected by the Registry of Bone Sarcoma of the American College of Surgeons. Omitting benign and metastatic tumors and inflammatory conditions, the author's chapters are devoted to Osteogenic Sarcoma, Ewing's sarcoma, Myeloma, Giant-cell Tumor and various miscellaneous forms. As is proper, osteogenic sarcoma receives the most detailed treatment; but Ewing's sarcoma will be probably read with more interest, on account of its novelty and unfamiliarity to those unacquainted with the Registry material. Its "specific clinical course" (often resembling osteomyelitis), its "typical gross anatomy" (smaller bones and skull and not at the ends, the "shells" of new-formed bone, metastases) and histology and its response to radiation are thought sufficient to establish it as a clinical entity. The warning that giant-cell tumors may become (or produce) malignant disease is also to be noted. E. K.

TEXTBOOK ON DISEASES OF THE SKIN AND SYPHILIS. By ALBERT STRICKLER, M.D., Professor of Dermatology and Syphilology, Temple University Department of Medicine. Pp. 689; 218 illustrations. Philadelphia: F. A. Davis Company, 1927.

TO one who views with not unmixed rejoicing the flood of dermatologic texts for which this country, perhaps more than any other has stood sponsor, the appearance of a new work of the type represented by the above is not a particularly encouraging event. Although the preface presents a laudable program, the author has not been successful, in the opinion of the reviewer, in carrying it through. Originality, which might chiefly serve as an excuse for a new text, is conspicuously lacking. The material is too extended for a compend and too condensed for an adequate scientific presentation. The differential tables, on which emphasis is apparently placed, fail in a number of instances to differentiate, at least in the mind of the reviewer. There are a few excellent illustrations and many poor ones exhibiting gross defects of photographic technique, to say nothing of an addiction to the wall-paper type of striking case which leaves the student with erroneous impressions. Syphilis is treated with a casualness which would be disconcerting even in a dermatologic compend. All things taken together, it is impossible to imagine a use for this text in medical teaching of the present day. A. B.

BOOKS RECEIVED.

Urography. By WILLIAM F. BRAASCH, M.D. Second edition. Pp. 480; 759 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $13.00. (To be reviewed later.)

Treatment of Venereal Disease in General Practice. By E. T. BURKE, D.S.O., M.B., CH.B. (GLAS.) Pp. 162, 8 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Diseases of the Newborn. By JAMES BURNET, M.A., M.D., F.R.C.P. (EDIN.). Pp. 275. New York: Oxford University Press American Branch, 1927. (To be reviewed later.)

The Diagnosis of Pancreatic Disease. By ROBERT COOPE, M.D., B.Sc., M.R.C.P. Pp. 112; 12 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

An Introductory Course in Ophthalmic Optics. By ALFRED COWAN, M.D. Pp. 262; 121 illustrations. Philadelphia: F. A. Davis Company, 1927. Price, $3.50. (To be reviewed later.)

Epidemic Encephalitis. By LEO M. CRAFTS, B.L., M.D. Pp. 237; 10 illustrations. Boston: Richard G. Badger, 1927. (To be reviewed later.)

The Ear, Nose and Throat in General Practice. By D. A. CROW, M.B., CH.B. (EDIN.). Pp. 150; 45 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Textbook of Pathology. By FRANCIS DELAFIELD, M.D., LL.D. and T. MITCHELL PRUDDEN, M.D., LL.D. Fourteenth edition. Pp. 1339; 850 illustrations. New York: Wm. Wood & Co., 1927. Price, $10.00. (To be reviewed later.)

Ophthalmoscopy, Retinoscopy and Refraction. By W. A. FISHER, M.D., F.A.C.S. Second edition. Pp. 291; 260 illustrations. Philadelphia: F. A. Davis Company, 1927. Price, $3.75. (To be reviewed later.)

The Tongue and Its Diseases. By DUNCAN C. L. FITZWILLIAMS, C.M.G., M.D., CH.M.F.R.C.S. (EDIN. and ENG.). Pp. 505; 172 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Clinical Case-Taking. By GEORGE R. HERRMANN, M.D., PH.D. Pp. 90; 8 illustrations. St. Louis, C. V. Mosby Company, 1927. Price, $1.50. (To be reviewed later.)

Minor Surgery. By ARTHUR E. HERTZLER, M.D., F.A.C.S. and VICTOR E. CHESKY, A.B., M.D., F.A.C.S. Pp. 568; 438 illustrations. St. Louis, C. V. Mosby Company, 1927. Price, $10.00. (To be reviewed later.)

Feeding and the Nutritional Disorders in Infancy and Childhood. By JULIUS H. HESS, M.D. Fifth edition. Pp. 566; 46 illustrations. Philadelphia: F. A. Davis Company, 1927. Price, $4.50. (To be reviewed later.)

The Rise and Fall of Disease in Illinois. Pp. 432; 31 illustrations. Published by the State Department of Health, 1927. Treated from the points of view of the various diseases of various cities and the growth of the department of public health.

Bronchoscopy and Esophagoscopy. By CHEVALIER JACKSON, M.D. Second edition. Pp. 457; 189 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $8.00. (To be reviewed later.)

Lectures on the Biologic Aspects of Colloid and Physiologic Chemistry. Mayo Foundation. Pp. 244; illustrated. Philadelphia: W. B. Saunders Company, 1927. Price, $2.50. (To be reviewed later.)

Diseases of the Skin. By ROBERT W. MACKENNA, M.A., M.D., B.CH. (EDIN.). Second edition. Pp. 452, 179 illustrations. Baltimore: Williams & Wilkins Company, 1927. (To be reviewed later.)

The Life and Work of Sir Patrick Manson. By PHILIP H. MANSON-BAHR, D.S.O., M.D., F.R.C.P. and A. ALCOCK, C.I.E., LL.D. Pp. 273; 12 illustrations. New York: Wm. Wood & Co., 1927. Price, $5.50. (To be reviewed later.)

The Essentials of Otology. By GEORGE BIRMINGHAM MCAULIFFE, A.B., M.D., F.A.C.S. Pp. 177; 46 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Diseases of the Mouth. By STERLING V. MEAD, D.D.S. Pp. 578; 303 illustrations. St. Louis: C. V. Mosby Company, 1927. Price $10.00. (To be reviewed later.)

Emergencies of a General Practice. By the LATE NATHAN CLARK MORSE, C.A.B., M.D., F.A.C.S. Revised by AMOS WATSON COLCORD, M.D. Second edition. Pp. 541; 311 illustrations. St. Louis, C. V. Mosby Company, 1927. Price, $10.00. (to be reviewed later.)

Healthy Growth. By ALFRED A. MUMFORD, M.D. Pp. 348; 29 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Everywoman a Nurse. By EDITH NEWSOME, S.R.N. Pp. 204; 31 illustrations. New York: Oxford University Press, American Branch, 1927.

Blood Pressure. Its Clinical Applications. By GEORGE WILLIAM NORRIS, A.B., M.D., HENRY CUTHBURT BAZETT, M.B., B.CH. (OXON.) F.R.C.S. (ENG.) and THOMAS M. MCMILLAN, A.B., M.D. Fourth edition. Pp. 387; 48 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $4.50. (To be reviewed later.)

Outlines of Pathology. By HORST OERTEL. Pp. 479; 132 illustrations. Montreal, Canada: Renouf Publishing Company, 1927. (To be reviewed later.)

The Ophthalmic Year Book. Volume XXIII. Edited by WILLIAM H. CRISP. Pp. 338. Chicago: Ophthalmic Publishing Company, 1927. (To be reviewed later.)

Getting Well and Staying Well. By JOHN POTTS, M.D. Pp. 223. St. Louis: C. V. Mosby Company, 1927. Price, $2.00.

Procedure Book. The Methodist Episcopal Hospital, Brooklyn, N. Y. Pp. 151. Price, $2.00.

The Queen Charlotte's Practice of Obstetrics. By J. BRIGHT BANISTER M.D., F.R.C.S., ALECK W. BOURNE, M.B., F.R.C.S., TREVOR B. DAVIES, M.D., F.R.C.S., L. CARNAC RIVETT, M.C., F.R.C.S., L. G. PHILLIPS, M.S., F.R.C.S. and C. S. LANE-ROBERTS, M.S., F.R.C.S. Pp. 629; 274 illustrations. New York: Wm. Wood & Co., 1927. Price, $7.00. (To be reviewed later.)

Manual of Chemistry. By W. SIMON AND DANIEL BASE. Thirteenth edition. Pp. 695; 55 illustrations. Philadelphia: Lea & Febiger, 1927. (To be reviewed later.)

An Introduction to Clinical Perimetry. By H. M. TRAQUAIR, M.D., F.R.C.S., ED. Pp. 264; 165 illustrations. St. Louis, C. V. Mosby Company, 1927. Price, $13.50. (To be reviewed later).

Potassium and Tartrates. By RALPH W. WEBSTER, PH.D., M.D. Pp. 168. Chicago: Commonwealth Press, 1927. Price, $2.50.

A Treatise on Orthopaedic Surgery. By ROYAL WHITMAN, M.D., M.R.C.S., F.A.C.S. Eighth edition. Pp. 1061; 954 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $9.00. (To be reviewed later.)

Tonic Hardening of the Colon. By T. STACEY WILSON, M.D., B.Sc. Pp. 210. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Krebs und seine Wahre Ursache. By J. WINKELHAGEN. Pp. 75. Munich: F. Bruckmann, 1927. Price about 70 cents. An attempt to explain cancer on the basis of individual, sex, racial disposition, etc., which in turn is thought to be developed by social poisons such as alcohol, tobacco, and coffee!

Gonococcal Infection in the Male. By ABRAHM L. WOLBARST, M.D. Pp. 237; 89 illustrations. St. Louis, C. V. Mosby Company, 1927. Price, $5.50. (To be reviewed later.)

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Extramedullary Hematopoiesis in Anemias.—Blood-making function of the spleen has been a problem that has been discussed backward and forward for many years. Physiologists and embryologists are agreed that the organ in fetal life is capable of producing blood cells. After birth it is held by some that this function reverts to the bone marrow alone. BRANNAN (*Bull. Johns Hopkins Hosp.*, 1927, **41**, 104) reviews the literature on the work which has been carried out experimentally and the autopsies that have been reported in some of the cases of severe anemia of childhood in which hemopoietic changes have been found in the organ. He then reports a case, with complete autopsy findings, in which the spleen showed foci of myeloid tissue, together with red, tumor-like growths in the hilus of the kidney, which was composed of all of the elements of hyperplastic bone marrow with a great predominance of red cells. The observation may be made that if hemopoiesis may occur in other organs than the spleen it may also occur in the spleen. In this particular case the myeloid foci would point to the spleen as being even more prone to assume the function of blood-cell formation than other organs. In adults the blood formation outside of the bone marrow has received very little recognition in this country. Two of the three cases that have been reported occurred at the Pennsylvania Hospital at the time Longcope was the pathologist at this institution and were reported by two of his assistants at that time. In Europe, quite a few cases have been observed. There seems to be a generally conceded opinion that myeloid elements are constantly present in the spleen. Blood-forming tissue elsewhere has not been noted except as a pathologic curiosity. Brannan's second case is in an adult who died after prolonged hemorrhage and sepsis who showed in the liver and spleen definite evidence of blood formation, especially in the capillaries of the liver. Blood forma-

tion occurred also in the broad ligaments, the first reported observation of this kind. Blood production may be found in the broad ligaments of children under apparently normal conditions. The two case reports presented by the author give added proof that blood cells may be formed outside of the bone marrow. This extramedullary formation of blood is apparently a compensatory process for bone marrow which may be exhausted or even when the bone marrow is hyperplastic. The origin of these early blood cells and foci is not definitely known. One school holds that the hematopoietic foci are metastatic; another school that it is autochthonous. This would seem to be the most logical explanation, as during intrauterine life the blood is normally formed in the liver, spleen, thymus and hemolymph nodes.

Exophthalmic Goiter and the Involuntary Nervous System.—The present paper by KESSEL and HYMAN (*Arch. Int. Med.*, 1927, **40**, 314) is the thirteenth in a series which was begun nearly five years go. The primary purpose of these authors was to study 50 unselected cases of fully developed exophthalmic goiter in order to determine the natural history of the disease without therapeutic measures of a specific nature. The thirteenth paper is a report of the 50 cases over a period of five years. In 31 of these cases they were able to follow the spontaneous course. In 19 the spontaneous course could not be completed, because 6 died, a mortality of 12 per cent, and 13 were lost from observation or received specific therapy, 8 of whom were operated upon and 1 of whom died. In the remaining cases it is of great interest to note that without any specific measures directed to the treatment of these patients, in more than half economic and social restitution occurred after the fourth month, continuing up to an average of fifty-seven months, and this despite the type of patients Kessel and Hyman were able to study—patients from the lower East Side of New York City who had to undergo the social discomforts and the physical activities of the very poor.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Urethral Diverticula.—NICHOLSON (*J. Urol.*, 1927, **18**, 145) claims that congenital diverticula are quite rare. Many cases reported as being congenital fall short of conclusive proof. Though the greater number of congenital diverticula occur in the penile urethra, they may occur at any point along the male urethra. Embryologic evidence is in support of congenital diverticula being entodermal in origin. Histo-

logic study of the diverticular wall may aid greatly in determining the etiology of the sac, but not its embryology. Congenital diverticula usually come to the physician's attention before the patient reaches adult life. Treatment of any diverticulum should be directed toward removing the sac and clearing up infection. Diagnosis in the ordinary case is not especially difficult. Frequently the most evident sign is tumor appearing upon voiding and afterward collapsing spontaneously or under external pressure.

Acute and Chronic Pancreatitis.—CULLEN and FRIEDENWALD (*Arch. Surg.*, 1927, **15**, 1) say that the incidence of both acute and chronic pancreatitis is far greater than has been recognized and as the symptomology of these conditions is usually indefinite, the correct diagnosis is too rarely made. In acute hemorrhagic pancreatitis, the onset is ushered in by a sudden violent pain in the epigastrium with signs of shock which may suggest rupture of a peptic ulcer, gall bladder or even of the appendix. The acute gangrenous form follows the hemorrhagic type in which the symptoms manifested have been of a milder or subacute form. The acute suppurative type in which abscesses are formed frequently ensues as a subsequent stage after either of the two types first named. Attention must be directed particularly to the significance of fat necrosis as an important accompaniment, especially of hemorrhagic and gangrenous pancreatitis and its value as a diagnostic sign at operation. The question of immediate surgical intervention has not been definitely decided. Many surgeons consider that it is best to delay until shock has somewhat subsided. In the study of chronic pancreatitis, the relation of this condition to cholecystitis and cholelithiasis is a matter of considerable interest. Although the symptoms are rarely definite, the bulky soft fetid and oily stools containing indigested fat and protein, aid in arriving at the diagnosis. In diagnosis, difficulty may be experienced in differentiating between cancer of the pancreas and chronic pancreatitis. In the prophylactic treatment of this condition, attention must be especially directed to the early removal of gall stones before complications have occurred.

Simple Uncomplicated Rotary Dislocation of the Atlas.—JACKSON (*Surg., Gynec. and Obst.*, 1927, **45**, 156) claims that uncomplicated rotary dislocation of the atlas occurs more commonly than is supposed and may be easily overlooked. If the lesion is not recognized and reduced it may result in sudden death from an increase in the dislocation or to the development of myelitis months or years after the injury. Rotary dislocation of the atlas is a distinct clinical entity presenting a characteristic history and symptoms with physical findings verifiable by Roentgen ray examination. The chief points in the history of the average case are history of an accident attended by the sudden application of an unexpected force in an oblique direction to the front or top of the forehead, inability to open the mouth beyond a very limited extent; difficulty in swallowing, due to injury of the first or second cervical nerves, which renders the pharyngeal plexus inefficient. Every effort should be made to reduce the dislocation including, if necessary, resort to open operation.

Ligamentous Injury About the Knee Joint with Report of Cases.—MURPHY (*Illinois Med. J.*, 1927, **52**, 69) says that in an anatomical consideration of the knee, a most remarkable quality is its strength and stability, which is consistent with its wide range of motion and with its mechanical disadvantage for the knee joint is a hinge joint with movement confined practically to one plane. The integrity of the knee joint lies in the splendid arrangement and strength of the ligaments, which surround it and fortify it against derangement. The principal ligaments about the knee are the internal lateral, the external lateral, the posterior capsular and the crucial ligaments. The principal tendons add strength to the joint while the joint is deepened by the semilunar cartilages which are attached around their peripheries to the ligaments which pass over the joint. The commonest injuries are ruptures of the ligaments. Diagnosis is made on the history of the injury, tenderness at localized points about the joint and the increasing pain upon bringing the respective injured tendons into play. Even the uncommon injury of fracture of the patella may be interpreted as a rupture of the quadriceps tendon, because the patella is in reality a sesamoid bone developed inside this tendon. In treating these ligamentous injuries as a class, conservative treatment may be given as the rule. We must take into consideration the fact that these ligaments are made up of white fibrous connective tissue, which is inelastic and therefore will not contract when severed. Therefore, when most ruptures occur, if the knee can be placed in a position to relax the injured ligament and allow the torn ends to approximate, the first and most important step in the treatment will have been accomplished. Operative interference is only to be resorted to when the severed ends cannot be approximated by manipulative measures.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Modern Treatment of Eczema in Infants and Children.—SCHLOTZ (*Arch. Ped.*, 1927, **44**, 601) states that infantile eczema is etiologically essentially a dietetic and systemic problem, but in the clinical control of it, the systemic and local treatments are of equal importance. The therapeutic failures in infantile eczemas are largely due to a stereotyped and uniform handling of cases, and a disregard for the individual therapeutic requirements of the different types of eczema. A greater accuracy in the diagnosis of the various types of eczema is possible on the clinical data alone and should be practised. Anaphylactic cutaneous food tests have not proved fully reliable and applicable as a routine procedure, and it should be applied in well-selected cases only. Phenol, sedatives and mechanical restraint devices are superfluous and injurious

and should not be used for the control of itching in infantile eczema. Crude coal tar and naphthalan are the least irritating and most effective drugs in chronic infantile eczema. Ultraviolet light and Roentgen ray are the best and most effective therapeutic agencies in the control of infantile eczema. The precision of modern diagnostic technique and the modern therapeutic resources have transformed infantile eczema from a reputed incurable and intractible disease to one well amenable to therapeutic control.

Parental Blood Serum in Measles Control.—Bivings and Dickson (*Arch. Ped.*, 1927, **44**, 629) report their observations on 23 cases in which parental or adult blood serum was given to measles exposures. Of these 14 were given complete protection, while 9 were caused to have a modified type of the disease. Dosage depended on age and the results desired. The older the child the larger must be the dose of the serum, in either preventing or modifying the disease. Larger doses are required for complete protection than are needed for modification. There probably is some difference in the protective power of serum of different individuals, and this will explain an occasional failure. In order to be effective the serum must be given within the first three or four days after exposure. The ideal that should be sought for is attenuation rather than complete temporary protection. There will be less objection on the part of parents if their own serum is used rather than a foreign serum. This also precludes the necessity for the Wassermann test. The serum is harmless insofar as reaction or ill effects are concerned. It is readily accessible at all times anywhere and can be used by any physician with a very simple technique.

Gastric Digestion.—Miles and Sohl (*Am. J. Dis. Child.*, 1927, **34**, 429) observed that dilute feeding mixtures leave the stomach at a more rapid rate than do those of greater concentration. The hydrogen-ion concentration of the stomach contents increases more rapidly with the dilute food than with a more concentrated milk of the same volume. The total acid secretion of the stomach is greater for the concentrated food of the same volume. The decrease in total buffer capacity of stomach contents at a given time is much greater in dilute than in the same amount of more concentrated mixtures. The buffer capacity of the stomach contents remains high until digestion is nearly completed. The hydrogen-ion concentration of gastric contents is relatively low when there is a short digestion period, a slow digestion, a large amount of feeding, or a concentrated mixture. The pH is a result of at least these four factors. Stomach contents with a high total buffer have a low hydrogen-ion concentration. Those with a low total buffer value are found to have a relatively high hydrogen-ion concentration when compared after the same digestive period. In stomach contents in which the hydrogen-ion concentration is high, the buffer value is low. In those with less acid values, the buffer value is high, except at the end of digestion. When large amounts of gastric contents are associated with high-buffer capacity, digestion is incomplete. The study of the buffer value of gastric contents in conjunction with measurement of pH and volume offers a new means of studying gastric digestion.

Tuberculosis in Childhood.—Gittings, Lathrop and Anderson (*J. Am. Med. Assn.*, 1927, **89**, 1415) believe that the prognosis in active pulmonary tuberculosis in childhood is bad in inverse proportion to the increasing age of the child. In cases with only a few small discrete pulmonary foci as the primary lesion involvement of the bronchial nodes give a relatively favorable prognosis under proper conditions. The possibility of cure is also good in involvements of the pleura without recognizable involvement of the lung. In children less than three years of age who give positive tuberculin tests without any clinical evidence of tuberculosis should show a large percentage of arrests, if they can be protected from reinfection and can be properly supervised. Infants with positive tuberculin reactions have a reasonably fair chance under similar conditions. In order to prevent massive or repeated infection, the child and more especially the infant must be separated from any active focus in the home. To prevent infection from becoming clinical disease, the principles involved in nonspecific constitutional treatment are recommended. In the treatment of active tuberculous disease of the lungs, glands and pleura, rest, fresh air, proper food and attention to the intestinal elimination are of the greatest importance. Ultraviolet radiation and exposure to direct sunlight are useful adjuncts to the treatment but must be applied with care and thought.

Progress of Breast Feeding in New York State.—Richardson (*J. Am. Med. Assn.*, 1927, **89**, 1487) was well pleased with the progress of breast-feeding increase in his state He gives an outline of the requirements of bringing about an increase of interest in this method of infant nutrition The first essential is that the physicians of the community must undertake the work. If this is not done the work will only be temporary or only for the length of the demonstration. Experience in the past has emphasized this tendency. While it is desirable to enlist the participation of many physicians in the community, it usually happens that it is due to the efforts of some one man that the work is actually made a success. Organized medicine in the community and the health department soon find that a breast-feeding demonstration is a platform on which both can work to the furtherance of a better mutual understanding. The rather interesting experience is that while the general practitioner usually welcomes the new teaching with enthusiasm, the pediatrician is harder to convince. In the smaller communities the obstetricians have been more enthusiastic in welcoming the breast-feeding demonstrations than they have in the larger cities where the proportion of babies leaving the maternity hospitals with artificial feeding already established is exceedingly high. Where the breast-feeding demonstration had been, the use of the proprietary foods and condensed milk drops to a remarkably low level, and the use of cow's milk in some form or other rises correspondingly.

Almond Whey Milk in Infantile Diarrhea.—Wittenberg (*Monatschr. f. Kinderheilk.*, 1927, **36**, 124) describes almond whey milk as a casein-free milk made from almond milk, calcium whey, maize flour and sugar. A liter of this has a caloric value of about 600. To make the calcium whey a liter of milk is boiled with 4 gm. of calcium lactate and thus the

casein is precipitated out. The whey which is separated by means of a filter cloth contains 0.3 per cent of albumen, and all the salts and sugar of the milk. Forty grams of almonds are allowed to stand in lukewarm water from twelve to twenty-four hours. They are then peeled and finely ground in an almond mill. With a gradual addition of water they are triturated in a bowl until a fourth of a liter has been poured in, when the mass is pressed through a linen bag. An equal amount of calcium whey is added to the almond milk thus obtained, and also a tablespoonful of maize or rice flour and two and a half lumps of sugar and the mixture is boiled. The finished almond milk contains 1.65 per cent of albumen, 6.6 per cent of sugar and 2.95 per cent of fat. It has almost the same composition as breast milk. It may be used to advantage as a temporary diet in mild and severe dyspepsia. In the most instances after using the almond whey milk the previously used diet was well tolerated. The diarrhea disappeared after using the almond milk whey for a period, during which there was a change in stool reaction and subsequently cessation of the diarrhea. Such a diet is useful in avoiding the dangerous starvation in treating diarrheas.

Nondiabetic Ketosis in Children.—WEYMÜLLER and SCHLOSS (*Am. J. Dis. Child.*, 1927, **34**, 549) studied the reactions of normal children and of children especially predisposed to ketosis, by means of diets of gradually increasing ketogenic values. The degree of ketosis judged by excretion of organic acid and acetone substances, which developed in the especially predisposed children, was notably greater than that which developed in the normal children. This observation serves as a chemical confirmation of their known clinical susceptibility. It was found that fasting for forty-eight hours resulted in a diminution of the severe grades of ketosis produced by high-fat diets in children subject to attacks of ketosis. This seems of interest since fasting in itself often causes ketosis of considerable degree. The mechanism involved was probably somewhat similar to that which occurs in diabetes. The patients were relieved immediately of the burden of high-fat and low-carbohydrate intake, and glucose from body protein was free to exert a maximum effect on fat metabolism. It seems probable that the lowered metabolism of starvation exerted a favorable influence. The fact that ketosis diminished during starvation despite abnormally low blood sugar has a bearing on two phases of the problem of nondiabetic ketosis. Recovery was probably not dependent on a large reserve of glycogen; and low blood sugar, either as an index of depleted reserve glycogen or due to some indirect influence, is not a determining factor in nondiabetic ketosis of children. In this study, two children subject to attacks of ketosis showed no excretion of acetone substances during a forty-eight hour period of fasting which followed high-carbohydrate diets. This observation has some bearing on the importance of defective storage of glycogen as a predisposing cause of cyclic vomiting and other forms of severe ketosis in children and would suggest that impaired storage of glycogen is not a constant etiologic factor. The fact that the blood sugar of these patients showed no marked reduction during the fast is definite confirmatory evidence that reserve glycogen was not depleted nor sugar mobilization impaired.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

STANLEY O. CHAMBERS, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

Food Allergy in Henoch's Purpura.—ALEXANDER and EYERMANN (*Arch. Dermat. and Syph.*, 1927, **16**, 322) present a series of cases illustrating what they believe to be aspects of food allergy associated with gastric and intestinal hyperperistalsis, localized edema and purpuric lesions on the skin. In a number of these cases the cutaneous tests for protein allergy were negative, but critical analysis and experimental adjustment of the diets led to the detection of the allergy-producing food, and removal of the food from the diet resulted in cure. Attacks of abdominal colic and smooth muscle spasm observed with the fluoroscope were noted coincidentally with the appearance of purpuric spots, edema and itching. Milk was responsible in one case; egg in a second, followed by a few purpuric spots in a few hours; rice in a third case. Osler's prophetic foreshadowing, "Before long, the anaphylactic key will unlock the mystery of these cases," is an interesting quotation.

Inoculation Tuberculosis of the Skin Simulating Sporotrichosis.—WIEN and CORNBLEET (*Arch. Dermat. and Syph.*, 1927, **16**, 312) describe a primary tuberculous lesion on the right little finger followed by lymphatic extension with multiple sporotrichoid nodules along the arm and involvement of the axillary glands. This case occurred in an adult.

Experiences in Gennerich's Endolumbar Treatment.—MÜLLERN-ASPEGREN (*Acta dermat.-ven.*, 1926, **7**, 391), using the original intraspinal technique of Gennerich, which involves direct introduction of a neoarsphenamin solution largely diluted with spinal fluid into the spinal canal, reaches the conclusion that intraspinal therapy has a definite favorable influence upon the course of neurosyphilis independent of the collateral treatment employed. He considers the special indications to include: (1) Syphilitic meningitis, where the infection was contracted more than one year previous, or less than one year if intravenous treatment has proved to be insufficient; (2) cerebrospinal or tabetic neurosyphilis in which there is still a marked meningeal phase. His results in general paresis were in the main unsatisfactory, but in 2 cases prolonged reduction in the spinal fluid to negative over a period of years with clinical remission apparently resulted from the treatment.

OBSTETRICS

UNDER THE CHARGE OF

NORRIS W. VAUX, M.D.,

CLINICAL PROFESSOR OF OBSTETRICS, JEFFERSON MEDICAL COLLEGE, PHILADELPHIA,

AND

CLIFFORD B. LULL, M.D.,

CLINICAL ASSISTANT IN THE OBSTETRICAL DEPARTMENT, JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Ovarian Therapy.—GRAVES (*J. Am. Med. Assn.*, 1927, **89**, 1308) shares in the keen disappointment to clinicians that the new knowledge gained of the function and properties of the female sex hormone has not led to a more effective therapy. He gives numerous reasons why the ovarian substance is in its present therapeutic form, nonpotent. First, the incretory power of the ovary in the normal adult woman is directed chiefly to the pelvic organs of reproduction, and has little bearing on the other functions of her general organism. This is demonstrated by the negligible harm done in removal of the organ and consequently the secretion. He does not place the ovary as an organ of the same vital significance as the suprarenals and the thyroid, and claims that its extracts are not as toxic as those of the other ductless glands. Ovarian preparations are comparatively inert in their influence on the general organism. The substance of the ovary in the performance of its function is one of a constantly changing existence, and he agrees with Fraenkel that in contrast with the other endocrine glands, all of which exercise a stable function, those of the ovary are in a continual state of transformation. In one phase of its function it stimulates hyperplasia, while at another time quite the reverse action may exist, and, therefore, any extract of the ovaries would contain the different phases of function and potency in reaction. This fact is well demonstrated by the inconsistency of the therapeutic action. The author takes up some of the outstanding abnormalities existing in women from puberty to the menopause. Among the outstanding ones are menstrual deficiency, including amenorrhea, hypomenorrhea and oligomenorrhea, and gives briefly and in detail the effect of the extracts of the female sex hormone on these cases. Further, abnormal uterine bleeding, dysmenorrhea and sterility. Each are discussed, many references given for the conclusions drawn. The recent work of Frank bears out the contention of the author, that the ovarian substance should theoretically be more stable than the corpus luteum extract. He concludes that for gynecologic purposes with abnormal uterine bleeding ovarian preparations, excluding the corpus luteum or at least those which include the whole organ with its follicular apparatus are the more rational choice. Whatever the preparation used, it is essential that it be comparatively fresh. Ovarian substance, the author feels, is a near-specific in treatment of

hot flashes, and vasomotor disturbances of the menopause. It is ineffective in permanent amenorrhea but useful in certain conditions of menstrual deficiency. It is ineffective in menorrhagias in metrorrhagias. Instances of pregnancy following ovarian therapy in sterility cases are common enough to suggest it occasionally in effecting a cure. Preparations of the whole ovary are more efficacious than corpus luteum alone. Fresh gland preparations are imperative and they are of sufficient clinical and experimental value, although admittedly feeble and inconstant in their action. He hopes that in future the research may be able to cause a potency in the use of ovarian substance in that it be a specific value in a limited number of functional pelvic disorders.

GYNECOLOGY

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Treatment of Rectovaginal Endometriosis.—The subject of adenomyoma of the rectovaginal septum, or, as it latterly has been termed, rectovaginal endometriosis, is one of intense interest at present to the gynecologist, largely due to the splendid investigative work of Sampson. These growths, although clinically benign, at times become so infiltrative in character and cause such obstructive symptoms as to resemble a malignant process. In well-marked cases the removal of the growth is often fraught with great danger but it is now known that by completely removing all ovarian tissue the growth will regress and will not have to be directly attacked, as evidenced by the experience of GRAVES (*Am. J. Obst. and Gynec.*, 1927, **13**, 728), who reports 2 cases of his own and 1 of Sampson's. In these cases he advises the performance of hysterectomy and the removal of both ovaries combined with a temporary colostomy. This method of treatment which has been so satisfactory is simple of execution and safe for the patient as compared with the formidable operation required in extirpating the growth. The temporary colostomy should be employed in severely obstructed cases until the constricting mass about the rectum is sufficiently atrophied or resorbed to permit of the normal function of the bowel. The type of colostomy which he recommends will close spontaneously in a few days after removal of the glass drainage tube, while the indurated mass in the pelvis may not entirely disappear but will diminish greatly in size and will cause no symptoms. Since endometriomas of all kinds reproduce both histologically and physiologically the uterine mucosa, I heartily agree with the author when he states that it is reasonable to suppose that unless it has undergone malignant change, the tumor

tissue, like that of the normal mucosa, should become atrophied after cessation of ovarian activity. I feel certain that if these principles are followed by surgeons generally, the mortality of the treatment of this desperate condition will be greatly lessened.

Endocrine Causes of Sterility in Women.—There has been considerable investigation of late into the endocrines and their relation to sterility, and in this country some of the most promising work has been done by FRANK (*Surg., Gynec. and Obst.*, 1927, **45**, 189), who summarizes his experiences in the treatment of this condition by saying that on the whole, with rare exceptions, it is most unsatisfactory. Obese patients are reduced by diet and, more rarely, by carefully supervised thyroid cures; those whose basal metabolism is normal are refractory to such treatment. Individuals with flabby musculature, low blood pressure, giving the impression of subnormality, must be improved by every roborant measure available. Under modern conditions which necessitate burning the candle at both ends, including the entire gamut of social visits, athletics, night life and tobacco, the patient's activities must be restricted. He believes that sun baths and quartz-lamp treatment, together with rest cures and overfeeding, should be tried out, but not persisted in to the extent of producing hypochondriasis. The sex life should be thoroughly investigated, but in the fewest instances is psychoanalysis indicated. Overindulgence is frequently found, because the uninstructed believe that the likelihood of fertilization is dependent upon the frequency of opportunity. Local treatment today is in its infancy. The attempts to improve the local nutrition of the uterus by means of stem pessaries is based upon the fallacious theory that the functional value of the uterus is solely dependent upon the amount of musculature it possesses. It should be recognized that its muscular development and turgescence under ordinary conditions are an indicator of the degree of ovarian activity. Recently attempts to stimulate the ovarian function by means of small doses of Roentgen ray applied to the ovarian region have been tried with a certain degree of success. The author warns that it must be borne in mind that radiation is a double-edged weapon, the difference between stimulating and depressive doses not being great, and that if the ovarian function is definitely on the decline even small doses of radiant energy may extinguish it completely. Finally, the stimulation of the ovarian function by means of the female sex hormone is still in its infancy but is becoming more and more promising. In his experimental work he has been able to show that the immature and inactive ovaries of infantile rats could be stimulated and made to become functional and remain cyclical by means of the exhibition of the female sex hormone. The product at present available for this therapy in the human female still awaits completion, because of the difficulty of purification, as well as stable preservation of this hormone. However, he is firmly convinced that we shall soon have this potent and invaluable weapon against sterility. It should prove of sovereign value unless infantilism or eunuchoidism of the sexual tract are of such a degree that the handicapped individual cannot respond to this specific hormonal influence. He is not sure that the masculine type will respond to the hormone treatment and must leave this question open for the time being.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Disturbance of the Optic Nerve Caused by Malignant Disease of the Sphenoid: Report of Two Cases.—The first case reported by WHITE (*Arch. Otolaryngol.*, 1927, **6**, 361) was a man, aged thirty-five years, who had a large central scotoma for colors. Vision of the right eye was 20/20, of the left eye 20/100. The fundi were negative. For the three weeks preceding examination he had had pain across the forehead and through the eyes. Roentgen rays showed marked erosion in the region of the sella turcica, the clinoid processes obliterated and the ethmoid and sphenoid moderately obscured. The biopsy was inflammatory. The neurologic examination was negative. The patient died one week later of meningitis. At autopsy Verhoeff made a diagnosis of carcinoma of the sphenoid bone and hypophysis. The second case was a man, aged forty-five years, who four months before the author's examination had had normal vision. Three weeks later it was 10/200 in the right eye, and still later was shadows only. The left eye was normal. The Roentgen ray showed that the right ethmoid and right antrum contained definitely thickened membrane. The right optic canal was larger than the left, the right being 5.5 and the left 5 mm. The physical and neurologic examinations were negative. The right antrum was opened, showing polypoid tissue, straw-colored fluid and pus. The septum was resected, the middle turbinate removed, the anterior wall of the sphenoid taken down and the ethmoids opened. Death occurred nearly three months later. The diagnosis was basal meningitis and carcinoma of the sphenoid. In his comment on the first case the author states that, in spite of the enormous destruction found at autopsy, the patient had only a moderate amount of pain and that only within the terminal four weeks. While he had noticed a loss of vision in one eye for eight months, he had marked blurriness only within the last month. The other eye was never involved, although both optic nerves were embedded in the growth. Neither of the nerves showed atrophy. In the second case the author notes the rapid unilateral loss of vision without optic atrophy. Neither of them had any of the usual symptoms associated with pituitary adenomas or temporal hemianopsia.

Protein Therapy in the Practice of Ophthalmology.—KEY (*Illinois Med. J.*, 1927, **52**, 318) states that the indications in which one may seem justified in administering protein therapy may be enumerated as follows: Pustule of the cornea, ulcus serpens and hypopyon keratitis, infection after penetration and panophthalmitis, idiopathic iritis and iridocyclitis (hidden focus of infection), keratomalacia and sympathetic

ophthalmia and for prophylactic purposes in certain cases. In regard to the selection of the most suitable, highly potential foreign protein available, antidiphtheritic serum as it is now prepared and concentreated offers pershaps the best form for administration to the human. Commercial products prepared for the purpose have not been shown to possess with any certainty a more reactive and potential effect than that of antidiphtheritic serum. The author has not noticed anaphylactic symptoms in more than 300 cases treated and doses have varied from 1000 to 5000 units. Larger doses have been given for therapeutic purposes and for prophylaxis, as much as 16,000 to 20,000 units having been employed by Verhoeff. Intramuscular injection is preferred to subcuticular, intravenous or oral administration. Two to 6 cc. (representing 2000 to 5000 units) of antidiphtheritic serum, varying with the age and weight of the patient, is injected at the earliest possible moment after local treatment, this dose being repeated or modified in forty-eight hours, depending on the reaction observed after the previous injection. A third and even fourth dose may be given at forty-eight hour intervals, without fear of anaphylactic symptoms, if the previous dose has failed to produce a local and quite active systemic effect. About 3200 units (4 cc.) is the average dose employed and seems to be just as effective as larger doses.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

A Rhinologic Study of Bronchial Asthma.—Bronchial asthma is clearly recognized today as a symptom and never as a disease. It is, however, only within the past fifteen years that any notable accomplishment has been made in the cause and prevention of this distressing condition. During the past decade very interesting studies have been reported by students of anaphylaxis and allergic sensitiveness, roentgenologists and rhinolaryngologists. After a historical consideration of asthma, BISHOP (*Ann. Otol., Rhinol. and Laryngol.*, 1927, **36**, 410) classifies asthmatic cases into *extrinsic* and *intrinsic*. The extrinsic group embraces those due to pollen, dust and food idiosyncrasy. The intrinsic group, comprising about half of the cases, includes bacterial and reflex causes. While the extrinsic asthmas are not within the function of the rhinologist for study or treatment, the intrinsic group offers a fruitful field of activity for rhinologic study and treatment. The bacterial group, with foci in tonsils, teeth or bronchi, has been extensively discussed by recent investigators, is quite generally understood, and has seemed to admit of little further discussion. The reflex

group, perhaps less understood, has seemed to warrant a rather detailed review of the nerve reflexes involved, as offering the most logical explanation of a certain type of bronchial asthma that has repeatedly been observed to promptly and permanently disappear following the correction of causative sources of irritation within the nares, notably in hyperplastic ethmoiditis. The author emphasizes that rhinologic treatment of asthma has been productive of results directly as it has been confined to the intrinsic cases. Whether directed to the removal of foci of infection in the nose, throat and bronchi in bacterial asthma, or to the correction of nasal defects in reflex asthma, the results obtained have compared favorably with those reported from any other form of treatment. After submitting observations on a large amount of clinical material, the author concludes that the results of 40 per cent completely relieved, 56 per cent improved and only 4 per cent unimproved, would seem to warrant the serious consideration, by rhinologists, of this problem of affording some measure of relief to the ever-increasing number of patients afflicted with this distressing condition.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

First Infection in Pulmonary Tuberculosis.—Facts established by Opie concerning first infections in tuberculosis would seem to indicate two distinct types of pulmonary involvement: one, a first infection predominating in children, affecting all portions of the lung with equal frequency, always associated with regional caseous lymph nodes; the other, a reinfection in adults, starting in the apex, tending to fibrosis and healing, never associated with caseous lymph nodes. SANTE (*Radiology*, 1927, **6**, 504) feels that the adult type might also be considered a first infection, the two different types being due to anatomic differences between children and adults. The adult type occurs at the periphery of the lung where the bronchial and pulmonary circulations mix. Lymph drainage from this region is in two directions: one, toward the hilum, giving rise to Dunham's fan; the other toward the pleura, giving rise to thickening of the pleura in the region involved and in the interlobe. Thickening of the pleura on the involved side was found in a large majority of incipient cases, and, though not pathognomonic of tuberculosis, is of distinct significance when associated with lesions in the apex.

Electrosurgical Treatment of Hemorrhoids.—Surgical diathermy is regarded as superior to excision, ligation or clamp and cautery by BIERMAN (*Physical Therapeutics*, 1927, **45**, 28). He uses either the monopolar or bipolar current, depending on the extent of the areas to be destroyed, and employs an electrosurgical clamp. This consists essentially of two active electrodes held parallel to each other and properly insulated to protect the operator. After anesthesia has been instituted, the hemorrhoid, whether it be internal or external, is grasped by means of an Allis clamp and held stretched while the jaws of the hemorrhoid clamp are approximated to its base. By means of a foot-switch the current is turned on. The hemorrhoid becomes coagulated across its base; the tissue is destroyed in the plane of the active electrodes held in the jaws of the clamp. The hemorrhoid is then cut off by means of scissors, scalpel or the high-frequency-cutting current. The thorough coagulation of the base permits immediate removal of the hemorrhoid, and avoids the foul odor caused by decaying dead tissue, contaminated by fecal organisms, when it is permitted to slough off. The electrosurgical clamp is superior to the ordinary clamp and cautery in that the cauterization is not superficial but occurs within the tissues embraced by the electric clamp. The destroyed area thus has sufficient depth to act as an efficient cover, holding the healthy margins of tissue firmly together and thoroughly protecting the healthy tissue beneath. During the two weeks or so before the coagulated area separates from the normal tissue the latter is preparing itself to act as a new covering surface, and when separation occurs the clean wound heals with great rapidity. As contrasted with the injection method, surgical diathermy insures more thorough and complete removal of superfluous tissue and avoids danger of embolic complications.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY, UNIVERSITY OF COLORADO.

Venous Angioma of the Cerebrum: Report of a Case with Necropsy.—MORSTER, DROUGHT, CARNEGIT, DICKSON (*J. Neurol. and Psychopath.*, 1927, **8**, 19) cite again the case recorded by C. Worster, Drought and Sir Charles Ballance in 1922. The case has since come to necropsy and the pathologic findings are recorded. The patient lived five years after the operation in 1921 and was free from epileptic seizures but had four attacks of slight numbness of the left arm and hand and the left side of the face. The subsequent course is not recorded excepting for the last ten days before his death. The pathologic findings revealed

many large dilated veins over the right cortex with the underlying brain substances much softened. The softening was most pronounced between the hemispheres. Death was considered due to subarachnoid hemorrhage from the angioma. The whole surface of the brain was hemorrhagic and appeared unduly soft. Features worthy of note are: (1) Jacksonian epileptic attacks with sensory aura beginning in the face; (2) no demonstrable change in cutaneous sensibility; (3) absence of fundus changes; (4) extremely large size of the veins forming the angioma; (5) improvement following operation; (6) death as result of hemorrhage from the angioma.

Tumeur du Lobe Frontal Droit Visible a la Radiographie.—MONIZ (*Rev. neurol.*, 1927, **2**, 277) presents a case of right frontal tumor with reproductions of radiographic plates showing tumor. The patient had atrophy of both optic nerves, anosmia and complained of headaches. There was an increase of albumin in the cerebrospinal fluid. The skull gave a cracked pot sound on percussion. The diagnosis of cerebral neoplasm was made, but it was impossible to localize it precisely in the absence of other neurologic or physical findings. Plainly visible by Roentgen ray was the shadow of a large solid tumor in the right frontal lobe together with a few smaller shadows posterior to it. The author considers the tumor as an angiolithic sarcoma or psamoma on the basis of its apparent attachment to the meninges. Surgical treatment was not considered because of the great depth and size of the tumor.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSOCIATE PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Concerning Formalin Precipitation in Tissues.—It has been repeatedly noted that pigment granules make their appearance in various tissues which have been fixed in formalin, and when observed in the organs of individuals residing in malarial districts offer some difficulty in differentiation from malarial pigmentation. SCHWARTZ and BIELING (*Ztschr. f. Exper. Med.*, 1926, **52**, 678) found that this pigmentation could be induced in experimental animals by various means. Although it has been suggested that the pigment probably had an origin from hemoglobin, it was found that this blood pigment was not the cause of the formalin precipitate. However the stroma of the red blood cells when introduced into experimental animals or when blood destruction, by various means, had been carried out *in vivo*, the pigment

made its appearance in various portions of the reticulo-endothelial system. It was furthermore found that the production of shock by means of sensitization of animals by various proteins would bring about the same effect. They conclude that the formalin pigment granules result from vital processes commonly having to do with the destruction of the blood elements. There is, however, no direct relation in their appearance with the blood pigments themselves. At times the deposit occurs in consequence to an antigen-antibody reaction resulting from foreign proteins. Whether the pigment may arise after death of the animal they do not discuss.

Experimental Infection with Single Virulent Bacteria.—The number of bacteria injected has usually been considered the chief factor in experimental infection. Investigators in Hahn's laboratory have reconsidered the well-recognized importance of the condition of "animalized" bacteria and have shown that with highly virulent microörganisms from infected animals a single bacterium is sufficient to initiate a fatal infection in animals. The technique for isolating individual organisms was that described by PETERFI and WAMOSCHER (*Ztschr. f. Hyg. u. Infektionskrankh.*, 1926, **106**, 191). MARX (*Ztschr. f. Hyg. u. Infektionskrankh.*, 1927, **107**, 472) investigated the streptococci and demonstrated that single streptococci injected into mice killed 32 per cent of the animals; two germs, 50 per cent; ten germs, 90 per cent. MARTOS (*Ztschr. f. Hyg. u. Infektionskrankh.*, 1927, **107**, 477), using similar methods with Bacillus anthracis, found that from 50 mice injected with single bacilli 14 became infected and that the percentage of positive results reached 100 when twenty bacilli were injected. It was further shown that with the smaller doses the death of the mice was delayed. When it is realized that a number of these isolated germs may be dead or weakened in vitality these results emphasize the importance of the condition of the germ at the time of the experimental infection and that the dose under optimal conditions may be reduced to the absolute minimum.

The Penetration of Infectious Agents into the Regional Lymph Glands and the Blood Stream after Cutaneous Infection.—In studying the problem of local as contrasted to general infection, SCHMIDT-OTT (*Ztschr. f. Hyg. u. Infektionskrankh.*, 1927, **107**, 441) infected a series of animals by the cutaneous, intracutaneous and subcutaneous routes with trypanosomes, spirochetes and the bacillus of swine erysipelas. After rubbing the lightly scarified skin of the scrotum with heavy suspensions of trypanosomes he found that the inguinal glands removed, emulsified and injected into mice contained the organisms two minutes after the infection. Using a similar technique he showed that spirochetes were demonstrable in the regional glands in fifteen minutes and the bacillus of swine erysipelas three minutes after an intracutaneous injection. He considered it probable that the local reaction, which usually occurs after a period when the microörganism can be regularly demonstrated in the blood stream, represents a general reaction with its greatest manifestation locally because there are more microörganisms or toxins in this local site.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Incidence of Endemic Thyroid Enlargement in Connecticut.—Olesen and Taylor (*U. S. Pub. Health Rep.*, 1926, **41**, 1695) have made a comparison of goiter in high school and grammar school students in Connecticut on one hand and in Cincinnati and Minnesota on the other, with the result that the condition in the eastern state was relatively uncommon, though 7 per cent of boys and 29.4 per cent of girls were affected. The problem in Connecticut is regarded as essentially that of adolescent girls, a general state-wide prophylaxis scarcely being indicated. The following is from the clinical point of view most pertinent: In view of the recently reported ill effects following iodin prophylaxis and treatment, it behooves those engaged in antigoiter activities not only to prescribe iodin in appropriately minute quantities, but also to be certain that iodin actually is indicated. It is just as important to know when to withhold iodin as when to administer it. Therefore, unless skilled treatment is available, it had best be withheld. Obviously, skillful treatment of thyroid conditions falls within the province of the especially qualified rather than the general medical practitioner.

Immunity to Pneumococcus Produced in Rats.—Ross (*J. Immunol.*, 1926, **12**, 219) found that rats fed on tissues of animals killed by penumococcus Type I show an increased resistance to intraperitoneal injection of the same germ. The protection seems to be type specific. Protective substances exist in the sera of the immunized animals. Reference is made to the very favorable immunization created by feeding pneumococci. An explanation is suggested for the fact that those types of pneumococci most commonly found in normal mouths are the cause of a minority of actual cases of lobar pneumonia. In further experiments, Ross (*J. Immunol.*, 1926, **12**, 237) found that rats which are fed the living pneumococci from 50 cc. culture per day are considerably more resistant to intraperitoneal injections of the same organism than are untreated control animals. The degree of protection is as good, although not so regular as that obtained when the tissues of animals killed by pneumococcus were fed. Rats which are fed the heat-killed pneumococci (80° C., two hours) in the same quantities show a decidedly inferior degree of immunity.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 21, 1927

The Effect of Temperature on Acidity of Skin.—H. C. Bazett and B. McGlone (from the Laboratory of Physiology, University of Pennsylvania). This study essayed to employ the intravital staining methods of Rous (*J. Exp. Med.*, 1925, **41**, 45) to observe if changes reported for blood *in vitro* by Stadie and Austin and their collaborators (*J. Biol. Chem.*, 1924, **60**, 191; *Medicine*, 1925, **4**, 275 and *J. Biol. Chem.*, 1925, **66**, 901) also occur *in vivo*, and if the vascular dilatation produced by heat can be dependent on the change in the reaction of the blood. White cats were decerebrated; the plane of section passed through the posterior colliculi and the anterior pontine margin. Observations were confined to the shaved forelegs. For injection, a 2 per cent solution of phenolsulphonephthalein was introduced into a vein of the hind leg. Circulatory arrest was effected by small cuffs of modified Riva-Rocci, which were adjusted lightly either above or at the elbow joint. Temperature effects were obtained by immersion in water in rectangular glass jars. Skin color was compared with that of La Motte standard tubes. The term pH is thus employed to express a comparable hue; while not regarded as an absolute value, it offers a means of expressing directional change and roughly the intensity of the change. On this basis the normal skin color compared with that of pH 7.4 to 7.6 in phenol-red standards at 20° C. Comparison of a leg in a cold bath with a control at 30° to 35° C. usually indicated a color slightly more purple in the "cold" leg. A temperature difference of the order of 8° to 12° was required to produce a detectable color difference. Thermocouple measurements showed that subdermal temperatures varied by less than 1° from that of the bath. In a bath of 12.5° at equilibrium the skin color corresponded to that of pH 7.5, the skin of the other leg 40.5° gave a comparable hue of pH 7.2. Corrections (Hastings and Sendroy, *J. Biol. Chem.*, 1924, **61**, 695) would indicate a pH difference of 0.5. During a circulatory arrest of ten minutes a barely perceptible shift to acidity was observed in the leg in the cold bath, while that in the warm bath developed a color more yellow than that of the standard of pH 6.8. Comparison of the persistence of the flush of a reactive hyperemia following varying periods of arrest of circulation with the amount and persistence of the acidity developed in the skin demonstrated that in general the degree of hyperemia and the acidity developed were parallel. At the higher temperatures both the hyperemic reaction and the acidity developed were intensified, but variations in temperature did not have a constant effect upon their duration. Following the production of a heat hyperemia in water at 40° to 42° C., immersion of one leg in cold water (18° C.) demonstrated that the hyperemia was more persistent in this leg than in the control at 36° C. (Lewis and Love, *Heart*, 1924, **13**, 27). Similar experiments

upon injected animals did not demonstrate any detectable acidity which would account for the persistence of this hyperemia. After small intradermal or subcutaneous injections of the indicator (0.6 per cent solution) in man, results similar in character but much less in intensity to those observed in cats were noted; however, the flush of a reactive hyperemia with immersion at 40° C. persisted longer than the suggestion of acidity. Since acidity and dilatation go parallel after release from circulatory arrest it is not justifiable at present to ascribe the dilatation entirely to the action of an histamine-like substance since the acid may be partly responsible.

Changes in Acid-base Equilibrium of Blood Caused by Hemorrhage.—Charles G. Johnston and D. Wright Wilson (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania). Severe hemorrhage causes a complicated series of physical and chemical changes in the body. There is a fall in blood-pressure and a diminished volume flow of blood. There may be a diminished transport of oxygen with a resultant accumulation of lactic acid. A diminution in alkaline reserve is a characteristic result. About two years ago, Dr. Bennett reported before this Society that arterial blood was more acid a half hour after a severe hemorrhage and this increased acidity persisted for at least four hours. In 1926, Gesell reported that the blood becomes alkaline after hemorrhage though it later becomes acid. The time intervals were not given. He had introduced two procedures differing from Dr. Bennett's, using anesthetized dogs instead of unanesthetized and using MnO_2 electrodes for determining the pH of blood instead of the hydrogen electrode. Sufficient objection may be raised both to the use of anesthetized animals and of MnO_2 electrodes to question whether the two types of experiments could be made to harmonize, so that the present authors decided to investigate the matter further. Withdrawing the blood from the heart by means of a needle required from one to five minutes to collect a sample of 100 cc. and about ten to thirty minutes to make a heavy bleeding. With this procedure we failed to obtain an alkaline swing. To obtain a more rapid bleeding a cannula was inserted in the femoral artery, using cocain as a local anesthetic. By this means samples could be drawn in less than a minute and heavy hemorrhages made in one to two minutes. With this procedure we usually obtained an alkaline swing immediately after hemorrhage, a result agreeing with Gesell's.

We determined pH (by means of the hydrogen electrode) total CO_2 and sometimes lactic acid. CO_2 tension and alkaline reserve at normal pH were calculated. For severe hemorrhages animals were bled 3 per cent or more of the body weight (30 to 40 per cent of the blood volume).

Twenty-eight experiments on 16 dogs yielded data which may be summarized as follows: In normal unanesthetized dogs, the arterial blood may become alkaline after severe hemorrhage. In half of our experiments the arterial blood was 0.15 to 0.13 pH higher while in half there were no changes outside of the error of the method. The arterial blood became more acid than normal within six minutes and thereafter the pH fell still further. The reaction of the blood was normal on the following day when a further hemorrhage caused more extreme swings.

We obtained arterial blood with pH ranging from 7.74 to 7.00. Hemorrhages of 2 per cent or less of the body weight caused no demonstrable change in the reaction of the blood.

Arterial CO_2 tension decreased after hemorrhage. This appears to be due to overaëration of the blood, which may be partly caused by increased ventilation of the lungs and partly by diminished CO_2 production in the body. When the decrease in carbonic acid (dependent on the CO_2 tension) is greater than the decrease in sodium bicarbonate the blood becomes alkaline.

The alkaline reserve fell and the lactic acid increased for some time after hemorrhage. The alkaline reserve was calculated at normal pH in order to get an estimate of the amount of alkali lost either by neutralizing acids diffusing into the blood or by passing out of the serum. As the loss of alkali was greater than the gain in lactic acid, alkali must have been lost in some other way.

Subdivision of Ultraviolet Spectrum by Simple Filters Including Solutions of Dyes.—S. Pond (from the Laboratory of Physiology of the University of Pennsylvania). The study of phenomena in living tissues accompanying the absorption of ultraviolet radiations frequently requires the isolation of a limited portion of the spectrum. While this may be accomplished in certain cases by monochromators or similar devices, the transmitted energy is usually so low as to be below the physiologic threshold. For greater percentage transmission and to cover greater areas, filters consisting of solutions or liquids in clear cells may be used. The container may be of clear fused quartz or glass with fluorite or quartz windows.

There are many liquids and solutions of organic and inorganic compounds which transmit visible light continuously (that is, have no absorption bands and are colorless in white light) and the transmission extends into the ultraviolet. The spectral point where absorption begins varies from compound to compound permitting a serial arrangement for differential use. A study of accessible materials has been made by the spectrographic method. The following substances which have been selected for their relatively steep absorption gradient in the ultraviolet are arranged as to the wave length where the photographic record of the mercury-vapor spectrum (quartz tube) ends (ca. 90 per cent absorbed or 10 per cent transmitted):

Liquids.	Thickness.	Angstrom units.
Methyl alcohol, CH_3OH ("absolute")	1 cm. thick	2028
Distilled water "conductivity"	"	2225
N aq. solution $NaHCO_3$	"	2253
10 N HCl (specific gravity = 1.19)	"	2302
95 per cent C_2H_5OH	"	2345
M/2 aq. solution $NaNO_3$	"	2482
M/4 aq. solution $CH_5N_3.HNO_3$ (guanidin)	"	2530
N/2 aq. solution KNO_3	"	2654
C_6H_6 ("thiophen free") benzole (0.883 specific gravity)	"	2804
$C_6H_4(CH_3)_2$.(1:2) xylol (specific gravity, 0.894)	"	2925

A second group of substances transmit discontinuously limited regions in both the visible and ultraviolet. Many examples of this group are colored solutions by virtue of their absorption in the visible

spectrum. The transmission band (or "window") in the ultraviolet is set off remarkably well by wide and deep absorption bands. From a number of spectrograms of such compounds a series has been arranged according to the points where the transmitted intensity of the last spectrographically recorded mercury-spectrum line is 10 per cent of its original value. In other words the region indicated is transmitted by the filter to a greater intensity than this value. Spectrophotometric curves have not yet been made. For reference purposes the nearest similar point in intensity value of the longer wave length regions is also indicated, thereby giving an idea of the width of the absorption bands between the two transmitted regions:

Substance.	Depth of strength of solution.	Transmission bands. (a) millimicra.	(b) millimicra.	
Potassium chromate	1 cm. m/6400 aq.	220–240	300	
Phenol	5 mm. m/1600 "	234–254	289	
Salicylic acid	1 cm. m/1000 alc.	244–277	334	
Fluorescein	5 mm. m/2000 "	254–260	296	
Quinin sulf.; N H_2SO_4: Alc. (3:1)	5 mm. 1:1000 "	264–289	366	
Picric acid	5 mm. m/1600 aq.	270–297	435	
Acridin golden yellow Schultz No. 602a	5 mm. 1:8000 "	270–303	366	
Auramine Stilbene yellow	5 mm. 1:4000 "	280–334	492	
Naphthol yellow Schultz No. 7	5 mm. 1:8000 "	278–366	492	Absorption band
Auramine	5 mm. 1:4000 "	289–297	492	
Xylene yellow	5 mm. 1:4000 "	289–313	492	
Auramine "O"	5 mm. 1:2000 "	289–303	492	
Filter yellow (EK CO)	5 mm. 1:4000 alc.	293–334	405	
Quinin	5 mm. m/1200 "	297–313	366	
Silbene yellow G	5 mm. 1:4000 aq.	293–335	492	
Tartrazine "O"	5 mm. 1:1000 "	297–313	545	
Dianil yellow 3G	5 mm. 1:4000 "	303–366	579	
Phosphine G (Schultz No. 606)	5 mm. 1:1000 "	313–366	660	

The Rôle of Hemolysis in Jaundice of the Newborn.—J. McK. Mitchell (from the Department of Pediatrics and the Pepper Laboratory of the University of Pennsylvania). Hofmeier first suggested an hematogenous origin for jaundice of the newborn. His theory received scant attention for many years. With the introduction of the van den Bergh test in 1913, work in this field received a great impetus.

The present experiment was designed to show whether there was a relation between hemolysis of the infant's cells by the mother's serum and the presence of jaundice. Mother's serum in dilutions of from 1 to 2 to 1 to 64 was set up against washed 5 per cent suspension of infant's cells in physiologic saline. These were incubated for ninety minutes at 37°. Out of 52 cases, 19 showed hemolysis; 17 of which were in jaundiced babies. Of 33 jaundiced babies over 50 per cent showed hemolysis. Similar but less marked results were obtained with cord serum. The fact that hemolysis occurred in 2 cases without jaundice is not construed as evidence against the specificity of the hemolysin, because jaundice must be considered as due to some factor operative in all babies. This is evidenced by the fact that every cord blood showed an indirect van den Bergh reading above normal and the subsequent van den Bergh on the infant's blood was still higher. The indirect van den Bergh reading checked well with the clinical estimation of the intensity of jaundice. In 58 cases the direct van den Bergh was never present. Increased fragility of the infant's red blood

cells was not a factor; nor was difference in the blood groups. In 141 cases, there was no identity between the lack of formation of the blood group in the baby and the presence of jaundice.

The author's conception of jaundice of the newborn is that it is due to destruction of the infant's cells by hemolysins which pass from the blood of the mother, through the placenta. If this conception is correct, the process must be operative *in utero*. Two questions are pertinent. Why are babies not born jaundiced? What is the explanation of the sudden increase of bilirubin after delivery? The assumption is that the placenta acts as an organ of excretion or storage as evidenced by its high iron content. After delivery the placenta ceases to function; hemolysis continues, its products heap up in the blood stream, give evidence of their presence in jaundice which fades as they are excreted or stored.

A New Method for the Determination of the Freezing Point of Solutions.—W. C. STADIE and W. F. SUNDERMAN (from the John Herr Musser Department of Research Medicine of the University of Pennsylvania). The apparatus makes it possible to transfer a solution slightly above its freezing point and without change in its composition to an equilibrium vessel where it comes in contact with ice. The temperature at equilibrium is read to 0.001° C. by a Beckman thermometer. Results with known solutions show the method to be reliable to ±0.003° C.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the article and should be complete, that is, author's name, title of article, journal, year, volume (in Arabic numbers) and page (beginning and ending).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL will be translated at its expense.